SEQUENTIAL DOMINO ONE-POT PROCESSES: 
SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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The Degree of Doctor of Philosophy

Department of Chemistry

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Declaration

I declare that this written submission represents my ideas in my own words, and where others' ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be a cause for disciplinary action by the Institute and can also evoke penal action from the sources that have thus not been properly cited, or from whom proper permission has not been taken when needed.

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My dearest parents and my brother for their love and affection. Without their support, I wouldn’t have been what I am today.
Dedicated to

*My Parents*
Abstract

One-pot synthetic processes are considered as convenient methods to synthesize organic molecules with high degree of complexity, without isolating intermediates. Such one-pot processes could be made possible by using one metal complex to catalyze a multiple reactions sequence or by adding various metal catalysts in a sequential manner to achieve multiple reaction sequence. These processes have proven to have several advantages over step-wise operations, as they avoid the isolation of intermediate species, thereby considerably reducing waste generation, increasing efficiency, minimizing the use of solvents, reagents, time and energy. Moreover, it was also found that in most cases the overall yields in one-pot processes are usually higher than those obtained from the corresponding step-wise operations. Herein, one-pot synthetic strategies have been developed for tetrahydroisoquinolines, cinnamate diesters, isochromenes, 2-benzoepinones and aryl-indenoindoles.

Synthesis of Tetrahydroisoquinolines:

The 1,2,3,4-tetrahydroisoquinoline 1 core is a ubiquitous structural entity existing in numerous plant based isoquinoline alkaloid natural products exhibiting a broad spectrum of biological activities such as antitumor, anti-microbial, anti-inflammatory, anti-HIV, anti-analgescic, neurotoxins and psychoactive properties. Representative examples are salsolidine, salsolinol, arizonine, O-methylpeyxylic acid, cherylline, latifine, Dopamine moieties include 6,7-DHBnTIQ, 3′,4′-DHBnTIQ, canadine, stepharinine, pronuciferine, erythrocarine (Figure 1).
The tetrahydroisoquinoline existence in natural products having interesting biological activities made synthetic chemists pay attention to their synthesis and numerous methods were developed by different research groups. These methods include the classical Pictet-Spengler condensation, Pomeranz-Fritsch-Bobbit cyclization, Friedel-Crafts reaction, cyclization of quaternary ammonium salts and metal mediated (or metal complex catalyzed) reductions of isoquinoline derivatives. Buchwald-Hartwig $\alpha$-arylation and norbornene mediated domino reactions are the recent methods reported in the literature, for the synthesis of tetrahydroisoquinolines using palladium catalysis.

With the interest to develop synthetic techniques based on transition metal catalysis, we have accomplished the concise stepwise synthesis of tetrahydroisoquinolines in good yields by using palladium catalyzed intramolecular Buchwald-Hartwig $\alpha$-arylation of $\beta$-amino esters as the key step. The $\beta$-amino esters which were required for the $\alpha$-arylation were achieved by simple aza-Michael addition of 2-bromobenzyl amines, which in turn were accomplished from readily available 2-bromobenzaldehydes (Scheme 1).
After step-wise accomplishment of tetrahydroisoquinolines, we made the method more efficient by employing a domino sequential one-pot neat aza-Michael addition followed by Buchwald-Hartwig α-arylation on secondary amines without isolating the intermediate β-amino ester. Overall, this method resulted in tetrahydroisoquinolines with yields comparable with stepwise syntheses of tetrahydroisoquinolines, where the final cyclization was conducted on the isolated β-amino ester (Scheme 2). Moreover, this method was successfully applied for the synthesis of novel aza-spirotricyclic ethers (Scheme 2). The results are explained in the chapter 1.
Synthesis of Cinnamate diesters, Isochromenes and 2-Benzoepinones:

The successful one-pot accomplishment of tetrahydroisoquinoline syntheses encouraged us to develop one-pot protocols. In this regard we have developed the efficient sequential one-pot intermolecular oxy-Michael addition and intermolecular Heck coupling for the synthesis of functionalized cinnamates. Bulky tert-butyl acrylate was identified as a more suitable Michael acceptor for initial oxy-Michael addition as it precludes the formation of undesired cross condensed ester over simple methyl or ethyl acrylate and acrylo nitrile (where acrylo nitrile interferes with the Pd-species during the reaction and decreases it’s activity). Most importantly, the current method was further extended to the sequential one-pot o-allylation with subsequent intramolecular Heck cyclization and successfully achieved the synthesis of isochromenes (Scheme 3).

![Scheme 3](image)

After the success of cinnamate diesters and isochromenes, the method was applied to the synthesis of 2-benzoepinones via sequential intermolecular Heck reaction, oxy-Michael addition and intramolecular degradation. When the cinnamate was subjected to the retro-Michael addition followed by intramolecular Michael addition to form iso-benzofuran we were surprised to obtain 2-benzoepinone as the major product (Scheme 4).
Interestingly these kinds of skeletons were found to be core structures in antibiotics such as xylarinol A and xylarinol B, and in natural products like ulocladorl and alterlactone which have interesting biological activities (Figure 2).

This observation lead us to develop the new one-pot strategy for the formation of 2-benzoepinone derivatives directly from ortho-bromo benzyl alcohols involving sequential one-pot oxy-Michael addition and Heck reactions followed by degradation. This one-pot protocol for 2-benzoepinones directly from primary ortho-bromo benzyl alcohols was successful only with ethyl acrylate as Michael acceptor (Scheme 5).
In the case of secondary alcohols with either ethyl acrylate or tert-butyl acrylate as and primary alcohols with tert-butyl acrylate Michael acceptors, the step wise degradation protocol from the corresponding diesters was followed in order to yield respective 2-benzoxepinones (Scheme 6). The results are detailed in the chapter 2.

**Synthesis of Aryl-indenoindoles:**

In addition to the one-pot protocols developed for tetrahydroisoquinolines and 2-benzoxepinones, we have also developed one-pot superacid mediated synthesis of novel 10-phenyl-5,10-dihydroindeno[1,2-b]-indoles, ubiquitous core structures of alkaloid natural products like yuechukene and borreverine. Significantly, such tetracyclic analogues were found to exhibit very good biological activities such as radical scavenging activity and anticancer activities (Figure 3).
The entire sequential process involved a domino intermolecular Friedel-Crafts alkylation and intramolecular acylation of simple and easily accessible ethyl cinnamates to furnish the indanones, followed by a Fischer indole reaction. Interestingly, this method enabled the synthesis of various dihydroindeno[1,2-b]-indoles possessing tertiary and quaternary centers at the 10th position (Scheme 7). The results are explicated in the chapter 3.

Scheme 7
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>Anal</td>
<td>analysis</td>
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<tr>
<td>Anhy</td>
<td>anhydrous</td>
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<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionization</td>
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<td>Ar</td>
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<td>aq</td>
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<td>CPD</td>
<td>carbon protan decoupling</td>
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<td>dt</td>
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<tr>
<td>DIPA</td>
<td>N,N-diisopropyl amine</td>
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<tr>
<td>DMF</td>
<td>N,N-dimethyl formamide</td>
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<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<td>equivalents</td>
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<td>Et</td>
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<td>ESI</td>
<td>electron spray ionization</td>
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<td>'pr</td>
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<td>Nuclear Magnetic Resonance</td>
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<td>quartet</td>
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<td>Rf</td>
<td>Retention factor</td>
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<td>room temperature</td>
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<td>septet</td>
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<tr>
<td>t</td>
<td>triplet</td>
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<tr>
<td>TEBAC</td>
<td>triethylbenzylammonium chloride</td>
</tr>
<tr>
<td>TEPA</td>
<td>triethyl phosphano acetate</td>
</tr>
<tr>
<td>'Bu</td>
<td>tertiary butyl</td>
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<tr>
<td>tert</td>
<td>tertiary</td>
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<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TfOH</td>
<td>trifluoromethanesulfonic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>UV</td>
<td>ultra violet</td>
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</table>
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CHAPTER I
SYNTHESIS OF TETRAHYDROISOQUINOLINES

1.1 INTRODUCTION:

The 1,2,3,4-tetrahydroisoquinoline 1 core is a ubiquitous structural entity existing in numerous plant based isoquinoline alkaloid natural products exhibiting a broad spectrum of biological activities such as antitumor,[1] anti-microbial,[1,2] anti-inflammatory,[3] anti-HIV[4] and anti-nalgesic[5] activities. Representative examples of such structures include salsolidine 2, isolated from plants of the genus Salsola, an inhibitor of monoamine oxidase,[6] which upon enzymatic transformation in the presence of N-methyl-transferase furnishes N-methyl salsolidine 3. Salsolinol 4, a catechol isoquinoline, was detected in rat and human brain tissue samples.[7] While N-methyl salsolinol 5, which was obtained from 4 upon the action of enzyme N-methyl-transferase, acts as neurotoxin.[7,8] Further, the natural product corypalline 6 from the plant Papaver bracteatum (Iranian poppy) is considered as the biosynthetic precursor of N-methylcorydaldine,[9] an alkaloid isolated from the plant Thalictrum fendleri and methylcorypalline 7, isolated from the embryo of loti (Nelumbo nucifera Gaertn).[10] On a similar basis, arizonine 8 was obtained by chromatographic separation of Carnegiea gigantean extract,[11] while, isoanhaloidine 9, isoanhalidine 10 and isoanhalamine 11 were obtained from North
American cactus *Lophophora williamsii*,\(^{[12]}\) these compounds have been recognized as the carriers of the core structure of isoquinoline.

![Chemical structures](Image)

**Figure I.1**
The methylated form of peyoxylic acid, O-methylpeyoxylic acid 12, was identified as a constituent of Peyote seeds and used as psychoactive North American entheogen. Anhalotine 13 is a quaternary nitrogen containing alkaloid in Lophophora williamsii, whereas, solifenacin 14 is a competitive cholinergic receptor antagonist and plays a critical role in the contraction of smooth muscle, thus controlling the urinary bladder smooth muscle tone. Substituted isoquinolines such as cherylline 15 and latifine 16, are phenolic Amaryllidaceae plant alkaloids isolated from several Crinum species, namely Crinum latifolium and Crinum powelli. The similar structures namely nomifensine 17 and dichlofensine 18 control the central nervous system activity and reduce serotonin and dopamine up-take mechanisms. Dopamine derivatized moieties like 6,7-DHBnTIQ 19 and 3′,4′-DHBnTIQ 20 are detected in mouse brain of which 20 induces parkinsonism in mice. Reticuline 21, an opium alkaloid found in various plants such as like Lindera aggregata, Annona squamosa and Ocotea fasciculata, possesses potent central nervous system depressing effects. The naturally occurring canadine 22 is a protoberberine class of alkaloid which blocks the calcium channel, while, stepharinine 23 and pronuciferine 24 belonging to proaporphine alkaloids, have been identified as the biosynthetic precursors of aporphine, a partial agonist of 5-HT1a. Erythrocarine 25 belongs to the family of widely distributed Erythrina plant alkaloids with interesting biological activities whereas, 6,6a-dihydrodemethoxygaudiscine 26 was obtained from the extract of the stem of Guatteriopsis friesiana (Figure I.1).

1.2 BACKGROUND:

Due to the relative abundance of the tetrahydroisoquinoline core in natural products having interesting biological activities, numerous methods were reported in the literature by different research groups. Some of the notable methods include classical Pictet-Spengler condensation promoted by acid, Pomeranz-Fritsch-Bobbit cyclization, Friedel-Crafts reaction and cyclization of quaternary ammonium salts. On the other hand, reductions of isoquinoline derivatives with metals like lithium, indium, zinc borohydride were employed for the construction of tetrahydroisoquinolines. In addition, a reasonably good number of
methods were developed based on catalytic reductions using metal complexes of rhodium, iridium, molybdenum, osmium. Moreover, reductions catalyzed by nickel, platinum (Adam’s catalyst: PtO₂), and Pd-C catalysts were also used for the tetrahydroisoquinoline synthesis. Also, processes like thermal cyclization, biomimetic synthesis and photo cyclization were used to prepare tetrahydroisoquinolines. Recently, the synthesis of tetrahydroisoquinolines was accomplished using palladium catalyzed intramolecular Buchwald-Hartwig α-arylation and norbornene mediated domino reactions.

I.2.1 Pictet-Spengler condensation:

A classical and transformation was discovered by Pictet and Spengler in 1911, in which the reaction of β-aryl ethyl amine with carbonyl compounds under acidic conditions leading to the formation of tetrahydroisoquinolines (Scheme I.1).

![Scheme I.1](image)

I.2.2 Pomeranz-Fritsch-Bobbit condensation:

The Pomeranz-Fritsch cyclization affords an efficient synthesis of isoquinolines, later modified by Bobbit, involving an acid catalyzed condensation of benzaldehyde with α-aminoethylacetal followed by catalytic reduction with H₂/Pt-C, which became a remarkable approach to achieve tetrahydroisoquinolines. Later, Rozwadowska et al successfully achieved the synthesis of salsolidine from the diethyl acetal precursor by using this Bobbit modification (Scheme I.2).
I.2.3 Friedel-Crafts reaction:

Yet another efficient synthesis of various tetrahydroisoquinolines 31 was proposed by Peerzada in 1997 by the Friedel-Crafts alkylation of N,N-dibenzylethlenediamines 30 in presence of the Lewis acid AlCl$_3$ (Scheme I.3).

I.2.4 Cyclization of quaternary ammonium salts:

Allyl benzyl dimethyl quaternary ammonium salt 32 underwent exo-trig cyclization upon treatment with polyphosphoric acid to furnish tetrahydroisoquinoline salt 33 in good yield (Scheme I.4).

I.2.5 Reduction by lithium metal:

The research groups of Costanzo and Remers reported the reduction of isoquinoline 34 with lithium in liquid ammonia to furnish the tetrahydroisoquinoline 1, albeit in poor yields (Scheme I.5).
I.2.6 Indium metal mediated reduction:

The co-workers of Moody\textsuperscript{[36a]} and Goti\textsuperscript{[36b]} developed indium metal mediated reductions of isoquinoline 34 and isoquinoline hydroxylamine 35 to tetrahydroisoquinoline 1, in the presence of aqueous ammonium chloride and ethanol as solvent (Scheme I.6).

I.2.7 Reduction with zinc borohydride:

Ranu et al in 1998 developed a convenient and simple protocol for the reduction of isoquinoline 34 to 1,2,3,4-tetrahydroisoquinoline 1 in the presence of a catalytic amount of N,N-dimethyl aniline under sonication conditions (Scheme I.7).

I.2.8 Reduction with complexes of rhodium and iridium:

The research group of Rosales applied rhodium and iridium catalysis for regioselective isoquinoline 34 to tetrahydroisoquinoline 1 (Scheme I.8).
I.2.9 Reduction with osmium complex:

Rosales group yet again developed another reduction protocol to form tetrahydroisoquinoline 1 from isoquinoline 34 by osmium metal complex (Scheme I.9).

![Scheme I.9](image)

I.2.10 Reduction with tris-trimethylphosphinomolybdenumhydride:

Parkin et al in 2008 reported the novel molybdenum catalysis for the conversion of isoquinoline 34 to tetrahydroisoquinoline 1 by means of co-ordination of the metal with isoquinoline followed by the reduction to tetrahydroisoquinoline 1 (Scheme I.10).

![Scheme I.10](image)

I.2.11 Nickel catalyzed deallylation:

N-allyl tetrahydroisoquinoline 36 was subjected to undergo N-deallylation by nickel catalyst in the presence of DIBAL-H as reducing agent to result in another effective method to produce the tetrahydroisoquinoline 1 (Scheme I.11).

![Scheme I.11](image)
**I.2.12 Reduction with Adams catalyst:**

Reduction of isoquinoline $34$ in the presence of PtO$_2$ was non selective and led to the formation of 5,6,7,8-tetrahydroisoquinoline $37$ along with the 1,2,3,4-tetrahydroisoquinoline $1$ (Scheme I.12).

![Scheme I.12](image)

**I.2.13 Reduction of isoquinoline-N-oxide:**

Zacharie et al reported a mild reduction procedure for the formation of tetrahydroisoquinoline $1$ from quinolinium-N-oxide $38$ by using palladium along with ammonium formate (Scheme I.13).

![Scheme I.13](image)

**I.2.14 Thermal cyclization:**

2-vinylbenzaldehyde $39$ and 3-aminopropanol underwent double cyclization reaction thermally and furnished the tetrahydroisoquinoline $1$ via the intermediate $40$ (Scheme I.14). The research group of Asao applied this concept in 2008, towards the synthesis of natural product cryptostylline II.

![Scheme I.14](image)
I.2.15 Biomimetic synthesis from $\beta$-aryl ethylamines:

Hailes et al recently reported a novel phosphate buffer mediated one-pot synthesis of tetrahydroisoquinolines 42 under mild reaction conditions starting from dopamine derivatives 41 (Scheme I.15).

![Scheme I.15]

I.2.16 Photo-cyclization:

Under photochemical conditions N-chloroacetylbenzylamine 43 in aqueous acetonitrile transformed into the corresponding cyclic amide 44 (Scheme I.16).

![Scheme I.16]

I.2.17 Intramolecular Buchwald-Hartwig $\alpha$-arylation:

Intramolecular $\alpha$-arylation of acyclic amide 45 to the cyclic amide 46, was achieved by Hartwig and group in 1998, albeit in poor yield. This might be due to the weak acidic methyl proton of an acetamide group (Scheme I.17).

![Scheme I.17]

In the sequence of designing strategies using palladium, Honda et al in 2001 reported the synthesis of 4-arylisoquinoline 48 via Pd-catalyzed intramolecular $\alpha$-
arylation as key transformation from a relatively more acidic methylene amide precursor 47 (Scheme I.18). The advanced intermediate 48 was used for the total synthesis of alkaloid natural product latifine 16.

Scheme I.18

Buchwald et al in 2002 reported a similar type of palladium catalyzed α-arylation on α-amino ester precursor 49 and achieved the corresponding tetrahydroisoquinoline derivative 50 in very good yield (Scheme I.19).

Scheme I.19

I.2.18 Norbornene mediated approach:

The research group of Mark Lautens in 2008, reported the palladium catalyzed norbornene mediated domino ortho-alkylation/alkenylation on the amide precursors 51 to form the functionalized tetrahydroisoquinolines 52 in excellent yields (Scheme I.20).

Scheme I.20
With the understanding of the science of synthesis of tetrahydroisoquinolines, and interest to develop synthetic methods based on transition metal catalysis, we have aimed at the synthesis of tetrahydroisoquinolines using palladium catalyzed intramolecular Buchwald-Hartwig α-arylation\[48\] as the key step. The strategy proposed involved a step-wise as well as the sequential domino one-pot method for the efficient synthesis of tetrahydroisoquinolines and the details are presented in the results and discussion section of this chapter.

I.3 RESULTS AND DISCUSSION:

I.3.1 Synthesis of Tetrahydroisoquinolines (Stepwise Approach):

In the designed retro synthetic analysis, we envisioned that the targeted 1,2,3,4-tetrahydroisoquinolines 56 could be achieved by Pd-mediated intramolecular α-arylation of β-amino esters 55. The β-amino esters 55, which in turn could be easily prepared from the readily available 2-bromobenzaldehydes 53 via reductive amination and aza-Michael addition 54 protocol (Scheme I.21).

\[
\begin{align*}
\text{COOR}^3 & \quad \text{COOR}^3 \\
\text{N} & \quad \text{N} \\
\text{R}_1 & \quad \text{R}_1 \\
\text{R}^2 & \quad \text{R}^2 \\
\text{56} & \quad \text{55} & \quad \text{53}
\end{align*}
\]

Scheme I.21

Thus, the synthetic sequence began with the preparation of 2-bromobenzaldehydes. Except for the 2-bromobenzaldehyde 53a, all the other ortho-bromobenzaldehydes 53b–53f were prepared using the literature reported standard bromination conditions.\[49\]
Table I.1: Synthesis of β-aminoesters 55a–55g via secondary amines 54a–54g.^[a]

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>Product</th>
<th>Yield</th>
<th>Isolated Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH3</td>
<td>HO</td>
<td>HO</td>
<td>CO2Et</td>
<td>55a</td>
<td>(88%)</td>
<td>(88%)</td>
</tr>
<tr>
<td>PH2</td>
<td>HO</td>
<td>HO</td>
<td>CO2Et</td>
<td>55b</td>
<td>(90%)</td>
<td>(90%)</td>
</tr>
<tr>
<td>MeO</td>
<td>HO</td>
<td>HO</td>
<td>CO2Et</td>
<td>55c</td>
<td>(86%)</td>
<td>(86%)</td>
</tr>
<tr>
<td>OMe</td>
<td>HO</td>
<td>HO</td>
<td>CO2Et</td>
<td>55d</td>
<td>(93%)</td>
<td>(93%)</td>
</tr>
<tr>
<td>MeO</td>
<td>HO</td>
<td>HO</td>
<td>CO2Et</td>
<td>55e</td>
<td>(95%)</td>
<td>(95%)</td>
</tr>
<tr>
<td>MeO</td>
<td>HO</td>
<td>HO</td>
<td>CO2Et</td>
<td>55f</td>
<td>(92%)</td>
<td>(92%)</td>
</tr>
</tbody>
</table>

^[a] isolated yields of the chromatographically pure products

The 2-bromobenzaldehydes 53a–53f were subjected for reductive amination with benzylamine/4-methylbenzylamine, in refluxing methanol and in the presence of a catalytic amount of acetic acid followed by portioned addition of sodium borohydride, furnished the secondary amines 54a–54g in good to excellent yields.
The formation and structure of the reductive amine 54 was evident from the spectral data of 54a. The absence of an absorption band due to carbonyl stretching of aldehyde group and the presence of a broad absorption band at 3334 cm\(^{-1}\) due to the N–H stretching in the IR spectrum indicated the formation of the secondary amine 54a. Aza-Michael addition reaction of secondary amines 54a–54g with the Michael acceptor ethyl acrylate in refluxing methanol furnished the corresponding β-aminoesters 55a–55g in excellent yields (84–95%, Table I.1).\(^{50}\)

In the \(^1\)H-NMR spectrum (Figure I.2.1), the absence of the aldehydic proton resonance, the presence of a doublet at \(\delta\) 7.58 resulting from one aromatic proton, a multiplet in the region \(\delta\) 7.48–7.24 due to seven aromatic protons, a doublet of doublet at \(\delta\) 7.16 due to one aromatic proton, two singlets at \(\delta\) 3.93 and 3.84 for the two benzylic methylene groups and one broad singlet at \(\delta\) 1.91 ppm for one proton attached to the nitrogen elucidated the structure of the secondary amine 54a. In addition, the 12 lines in \(^{13}\)C-NMR spectrum (Figure I.2.2), showing the presence of three quaternary carbon resonances at \(\delta\) 140.0, 139.1 and 124.0 due to three aromatic carbons, nine aromatic methine carbons at \(\delta\) 132.8, 130.4, 128.6, 128.4, 128.2, 127.4 and 127.0 & two methylenes at 53.1 and 53.0 ppm confirmed the structure of the secondary amine 54a.

Aza-Michael addition of secondary amines 54a–54g with the Michael acceptor ethyl acrylate in refluxing methanol furnished the corresponding β-aminoesters 55a–55g in excellent yields (84–95%, Table I).\(^{51}\) The β-aminoesters 55 were confirmed from the spectral data analysis of 55a. The absence of the stretching absorption band due to N–H group and presence of the strong absorption band at 1731 cm\(^{-1}\) due to the C=O stretching frequency of the ester group, in the IR spectrum indicated the formation of the β-aminoester 55a. In the \(^1\)H-NMR spectrum (Figure I.3.1), absence of the N–H proton resonance, the presence of two doublet of doublets at \(\delta\) 7.48 and 7.40 due to two aromatic protons, a multiplet in the region \(\delta\) 7.30–7.08 account for the six aromatic protons, a doublet of doublet of doublet at \(\delta\)
6.99 due to one aromatic proton, a quartet at δ 3.99 due to two protons of O-methylene, two singlets at δ 3.61 and 3.54 for two N-methylene

Figure I.2.1: $^1$H-NMR (400 MHz) spectrum of 54a in CDCl$_3$

Figure I.2.2: $^{13}$C NMR (100 MHz) spectrum of 54a in CDCl$_3$
groups, two triplets at δ 2.76 and 2.43 for two methylene groups, and one triplet at δ 1.11 ppm for three protons of the methyl group illustrated the structure of the β-aminoester 55a. In the 17 lines 13C-NMR spectrum (Figure I.3.2), the presence of

![Figure I.3.1: 1H-NMR (400 MHz) spectrum of 55a in CDCl3](image1)

![Figure I.3.2: 13C NMR (100 MHz) spectrum of 55a in CDCl3](image2)
one quaternary carbon resonance at δ 172.4 due to one ester carbonyl, and three quaternary carbon resonances at 139.0, 138.4 and 124.2 and the three aromatic carbons, respectively, nine aromatic methane carbon atoms at δ 132.5, 130.5, 128.7, 128.2, 128.1, 127.2 & 126.9 and five methylenes at δ 60.3, 58.2, 57.4, 49.4 and 32.6 and a methyl at δ 14.1 ppm confirmed the structure of β-aminoester 55a.

The β-aminoesters 55a–55g, the key intramolecular Buchwald-Hartwig α-arylation of the ester 55a was explored under different set of reaction conditions and the results are summarized in Table I.2. Therefore the treatment of the aminoester 55a with Pd(dba)₂ (5 mol%) in the presence of N-[2’-(dicyclohexylphosphino)-1,1’-biphenyl-2-yl]-N,N-dimethylamine ligand (10 mol%) with NaHMDS (4 equiv) as base in refluxing THF, failed to furnish the product 56a, and led to the recovery of starting material 55a (entry 1, Table I.2). Upon replacing the base NaHMDS with tBuOK (4 equiv) and without altering the catalyst, ligand and solvent parameters, led to the isolation of starting material 55a (entry 2, Table I.2). On the other hand, changing the ligand to PPh₃ (10 mol% or 20 mol%), use of different bases such as tBuOK (4 equiv) and Cs₂CO₃ (2 equiv), in DMF at 80 °C for a prolonged duration of 24 h, identical outcome was observed (entries 3–5, Table I.2). The reaction under microwave irradiation using toluene as solvent at 70 °C for 1 h also failed to furnish the product (entry 6, Table I.2). Interestingly, increasing the temperature and time to 110 °C and 3 h, respectively, afforded the expected product 56a in a moderate yield of 40% (entry 7, Table I.2). The use of K₂CO₃ in toluene at 70 °C for 24 h yielded no product (entry 8, Table I.2), however, at an elevated temperature and increased time gave the isoquinoline product 56a, albeit, in moderate yield 43% (entry 9, Table I.2). Interestingly, the reaction with K₃PO₄ as the base in hot toluene afforded the isoquinoline product 56a in 35% yield along with acid resulting from the hydrolysis of the ester, (entry 10, Table I.2). On the other hand, use of Pd(OAc)₂/BINAP as a catalyst in combination with tBuOK in anhydrous toluene and use of Pd(OAc)₂/PPh₃ with tBuOK/NaHMDS in anhydrous THF were unsuccessful and produced the corresponding acid, which might have resulted from the saponification of the ester 55c (entries 11–13, Table I.2). The generation of the
acid was however not clear as it was unlikely to form during neutral workup. Significant improvement in the yield of product 56a was observed, when the reaction was performed with Cs$_2$CO$_3$ in toluene at 120 °C (entry 14, Table I.2). Gratifyingly, 10 mol% of the catalyst Pd(OAc)$_2$ and 20 mol% of the ligand PPh$_3$, in the presence of Cs$_2$CO$_3$ at 80 °C for 24 h, furnished the intramolecular α-arylated tetrahydroisoquinoline product 56a in very good yield 82% (entry 15, Table I.2). Furthermore, the use of 10 mol% of Pd[PPh$_3$]$_4$, Cs$_2$CO$_3$ (2 equiv) in toluene at 80 °C for 24 h, afforded the product 56a in good yield 68% (entry 16, Table I.2).

**Table I.2:** Optimization of reaction conditions for the synthesis of 1,2,3,4-tetrahydroisoquinoline 56a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd]</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>yield 56a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(dba)$_2$</td>
<td>L$^\alpha$ (10)</td>
<td>THF</td>
<td>NaHMDS (4)</td>
<td>65</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)$_2$</td>
<td>L$^\alpha$ (10)</td>
<td>THF</td>
<td>tBuOK (4)</td>
<td>65</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)$_2$</td>
<td>PPh$_3$ (10)</td>
<td>DMF</td>
<td>tBuOK (4)</td>
<td>80</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(dba)$_2$</td>
<td>PPh$_3$ (20)</td>
<td>DMF</td>
<td>Cs$_2$CO$_3$ (2)</td>
<td>80</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pd(dba)$_2$</td>
<td>PPh$_3$ (20)</td>
<td>DMF</td>
<td>Cs$_2$CO$_3$ (2)</td>
<td>80</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$ (2)</td>
<td>toluene</td>
<td>Cs$_2$CO$_3$ (3)</td>
<td>70</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$ (2)</td>
<td>toluene</td>
<td>Cs$_2$CO$_3$ (3)</td>
<td>110</td>
<td>3</td>
<td>40</td>
</tr>
</tbody>
</table>
Unless otherwise noted all the reactions were carried out under anhydrous and inert atmospheric conditions.

Isolated yields of chromatographically pure products.

N-[2'-(Dicyclohexylphosphino)-1,1'-biphenyl-2-yl]-N,N-dimethylamine was used as the ligand.

Corresponding acid resulting from the hydrolysis of the ester is isolated.

Out of all conditions from the Table I.2, the conditions of entry 15 were the best; therefore, these conditions were applied on other \( \beta \)-aminoesters 55b–55g to check the scope and generality of the method. The method was found to be successful on all the esters 55 and yielded the products 56b–56g containing simple to electron rich bromoaryl moieties, in very good yields (70–87%), as summarized in the Table I.3.

The presence of the strong absorption band at 1730 cm\(^{-1}\) due to the C=O stretch of the ester group in the IR spectrum indicated the formation of the 1,2,3,4-tetrahydroisoquinoline 56a. In the \(^1\)H-NMR spectrum (Figure I.4.1), the

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)(_2)</th>
<th>PPh(_3)</th>
<th>Toluene</th>
<th>K(_2)CO(_3)</th>
<th>Temp</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Pd(OAc)(_2)</td>
<td>PPh(_3)</td>
<td>Toluene</td>
<td>K(_2)CO(_3)</td>
<td>70</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)(_2)</td>
<td>PPh(_3)</td>
<td>Toluene</td>
<td>K(_2)CO(_3)</td>
<td>110</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)(_2)</td>
<td>PPh(_3)</td>
<td>Toluene</td>
<td>K(_3)PO(_4)</td>
<td>80</td>
<td>24</td>
<td>35(d)</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)(_2)</td>
<td>BINAP</td>
<td>Toluene</td>
<td>(^1)BuOK</td>
<td>120</td>
<td>24</td>
<td>(_)(d)</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)(_2)</td>
<td>PPh(_3)</td>
<td>THF</td>
<td>(^1)BuOK</td>
<td>65</td>
<td>24</td>
<td>(_)(d)</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)(_2)</td>
<td>PPh(_3)</td>
<td>THF</td>
<td>NaHMDS</td>
<td>65</td>
<td>24</td>
<td>(_)(d)</td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)(_2)</td>
<td>PPh(_3)</td>
<td>Toluene</td>
<td>Cs(_2)CO(_3)</td>
<td>120</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td>15</td>
<td>Pd(OAc)(_2)</td>
<td>PPh(_3)</td>
<td>Toluene</td>
<td>Cs(_2)CO(_3)</td>
<td>80</td>
<td>24</td>
<td>82</td>
</tr>
<tr>
<td>16</td>
<td>Pd[PPh(_3)](_4)</td>
<td>No</td>
<td>Toluene</td>
<td>Cs(_2)CO(_3)</td>
<td>80</td>
<td>24</td>
<td>68</td>
</tr>
</tbody>
</table>

\(a\) Unless otherwise noted all the reactions were carried out under anhydrous and inert atmospheric conditions. \(b\) Isolated yields of chromatographically pure products. \(c\) N-[2'-(Dicyclohexylphosphino)-1,1'-biphenyl-2-yl]-N,N-dimethylamine was used as the ligand. \(d\) Corresponding acid resulting from the hydrolysis of the ester is isolated.
presence of a multiplet in the region δ 7.31–7.05 due to eight aromatic protons, one doublet of doublet at δ 6.95 due to one aromatic proton, a multiplet in the region δ 4.15–3.98 due to two protons of the O-methylene group, one doublet of doublet at δ 3.77 due to one methine proton attached to carboxylic ester, four doublets at δ 3.70, 3.64, 3.58 and 3.53 for four protons of two N-methylene groups, two doublet of

Table I.3: Scope and applicability of Buchwald-Hartwig α-arylation on β-amino esters 55b–55g.

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>Pd(OAc)2 (10 mol%)</th>
<th>PPh3 (20 mol%)</th>
<th>Cs2CO3 (2 equiv)</th>
<th>Toluene, 80 °C, 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56a</td>
<td>N</td>
<td>N</td>
<td>Bn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56b</td>
<td>N</td>
<td>N</td>
<td>Bn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56c</td>
<td>N</td>
<td>N</td>
<td>Bn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56d</td>
<td>N</td>
<td>N</td>
<td>Bn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56e</td>
<td>N</td>
<td>N</td>
<td>Bn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56f</td>
<td>N</td>
<td>N</td>
<td>Bn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56g</td>
<td>N</td>
<td>N</td>
<td>Bn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*yield is based on the recovery of the starting material

doublets at δ 3.09 and 2.77 for two protons of methylene group and one triplet at δ 1.12 ppm due to three protons of the methyl group elucidated the structure of 1,2,3,4-tetrahydroisoquinoline 56a. In the 17 lines from the 13C-NMR spectrum (Figure I.4.2), the presence of a quaternary carbon resonance at δ 173.1 due to the ester carbonyl, three quaternary carbon resonances at 138.0, 135.1 and 131.5 for the three aromatic carbons, respectively, ten aromatic methines at δ 129.2, 129.0, 128.2, 127.2, 126.8, 126.6, 126.2 and 45.4, four methylene carbons at δ 62.2, 60.8, 56.0 and 52.9 and a methyl at δ 14.1 ppm confirmed the structure of 1,2,3,4-tetrahydroisoquinoline 56a.
I.3.2 Synthesis of Tetrahydroisoquinolines (Sequential One-Pot Approach):

Certainly, sequential/domino one-pot methods hold advantages over step-wise methods. For example, such transformations, avoids the isolation of intermediates, minimizes the amount of waste generation, improves strategic
efficiency, requires less amount of time, and diminishes the use of number of solvents and reagents. In this regard, after accomplishment of tetrahydroisoquinolines 56a–56g in a step-wise strategy, we became interested in making the method more efficient by employing a domino one-pot aza-Michael addition followed by Buchwald-Hartwig α-arylation on secondary amines 54 without isolating the intermediate Michael addition product 55 (Scheme I.22).

![Scheme I.22](image)

The secondary amine 54a was chosen as a model for this study of domino one-pot aza-Michael addition followed by Pd-catalyzed intramolecular Buchwald-Hartwig α-arylation method. The reaction of secondary amine 54a with the Michael acceptor ethyl acrylate, Pd-catalyst [Pd(OAc)$_2$/PPh$_3$], and Cs$_2$CO$_3$, in toluene at 80 °C for 24 h gave the final product 56a, albeit in poor yield 15% (Scheme I.23). The poor yield of 56a might be due to the formation of aryl palladium species through insertion into the C-Br bond of the aryl bromide in competition to aza-Michael addition of ethyl acrylate.

![Scheme I.23](image)

Since, the above direct domino one-pot method was found inferior to step-wise method, we thought that an alternative aza-Michael addition followed by in-
situ treatment of the β-amino ester intermediate 55a for subsequent Pd-catalysed α-arylation may help to improve the yield of the end product 56a. The overall idea is to allow the smooth and complete formation of the initial Michael addition intermediate product 55a in an uninterrupted fashion, so that the overall yield of target product 56a would be increased by eliminating possible competitive reactions. Hence, it was important to identify the suitable reaction conditions for the aza-Michael reaction that would also be amenable for subsequent intramolecular palladium catalyzed α-arylation. Since, the Pd-catalyzed intramolecular α-arylation was smooth in toluene, the aza-Michael addition was explored with the secondary amine 54a using varying amounts of ethyl acrylate and the Cs₂CO₃, in hot toluene (50 °C and 80 °C). However, these trials furnished the β-aminoester 55a in poor to moderate yields (entries 1 to 4, Table I.4). Similar results were obtained by conducting the reaction at increased temperature (100 °C) in toluene without Cs₂CO₃ (entries 5 & 6, Table I.4). Interestingly, there was an improvement in the yield to (60%) upon using xylene as the solvent at high temperature 130 °C (entry 7, Table I.4). Alternatively, the reaction of amine 54a with ethyl acrylate without using any solvent (neat conditions) under microwave irradiation was also found to be less progressive (entry 8, Table I.4). Similarly, conventional heating of the secondary amine 54a and ethyl acrylate (1.5 equiv) without the base and xylene at 110 °C for 48 h, furnished the β-amino ester 55a in poor yield (entry 9, Table I.4). A low yield of the intermediate β-amino ester 56a might be attributed due to low boiling point of ethyl acrylate (100 °C), as it may escape from the reaction vessel. Therefore, it was envisioned that excess equivalents of the Michael acceptor ethyl acrylate might help to improve the yield of 55a. As expected, the reaction with excess (5 equiv) of ethyl acrylate at 110 °C for 48 h, showed 100% conversion to the intermediate β-amino ester 55a, which was on in-situ intramolecular Pd-catalyzed α-arylation, resulted the tetrahydroisoquinoline product 56a, albeit in moderate yield 43% (entry 10, Table I.4). Moderate yield of the tetrahydroisoquinoline 56a, was probably due to the intermolecular intrusion of excess Michael acceptor ethyl acrylate with the
Table I.4: Optimization of the one-pot reaction conditions for the synthesis of 1,2,3,4-tetrahydroisoquinoline 56a.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ethyl acrylate (equiv)</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield of 55a (%)</th>
<th>Toluene (mL)</th>
<th>Time (h)</th>
<th>Yield of 56a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>toluene</td>
<td>80</td>
<td>48</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>toluene</td>
<td>50</td>
<td>24</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>toluene</td>
<td>50</td>
<td>48</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
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<td>100&lt;sup&gt;e&lt;/sup&gt;</td>
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<sup>a</sup> Isolated yields of chromatographically pure product 55a and not subjected to the subsequent Pd-catalyzed α-arylation. <sup>b</sup> The product 55a was not isolated and the complete conversion of secondary amine 54a to product 55a was confirmed by TLC. <sup>c</sup> Base omitted in these attempts. <sup>d</sup> Both base and solvent omitted in these entries, only neat reaction conditions were employed. <sup>e</sup> Reaction was performed on 100 mg scale of secondary amine 54a. <sup>f</sup> Reaction performed on one mmol scale of secondary amine 54a. <sup>g</sup> Excess ethyl acrylate was removed under vacuum (10<sup>2</sup> mbar) just before the addition of Pd-catalyst, base and solvent, for subsequent Pd-catalyzed α-arylation. <sup>h</sup> Isolated yields of chromatographically pure product 56a.
intermediate aryl Pd-species of β-amino ester during the cyclization. Upon dilution of the reaction mixture with excess of solvent, after the complete formation of the β-amino ester 55a, and subjecting it for further cyclization, slightly improved the yield of tetrahydroisoquinoline product 56a (entry 11, Table I.4), but still concluded the interference of excess ethyl acrylate, which was still present in the reaction mixture. Finally, it was decided to eliminate of excess ethyl acrylate in order to avoid its interference with aryl Pd-species of β-amino ester 55a. Therefore, after formation of β-amino ester 55a, excess of ethyl acrylate was removed under mild vacuum (10⁻² mbar) and then subjected for subsequent intramolecular Buchwald-Hartwig α-arylation. These conditions were quite successful and furnished the tetrahydroisoquinoline product 56a in good yield 77%. These results have been detailed in the entry 12, Table I.4, wherein, the amine was used on a 1 mmol scale with 5 equivalents of ethyl acrylate for 24 h. The overall yield of the 56a (77%) was found to be as good as in stepwise formation of 56a (72%), which was calculated from the 82% of intramolecular α-arylation and 88% Michael addition reactions, respectively.

The optimized conditions (entry 12, Table I.4) were thus applied to the other secondary amines 54b–54i with various other Michael acceptors (methyl, ethyl, tert-butyl acrylates) were also tried. In general, these results were quite similar to that obtained for 54a, and furnished the tetrahydroisoquinolines 56 having simple to electron donating functionalities on aromatic rings, in very good yields (Table I.5). It was observed that in case of ethyl and methyl acrylates the aza-Michael reaction was completed in 24 h, whereas, in case of tert-butyl acrylate it took up to 48 h and succeeding Pd-catalyzed α-arylation was completed in 24 to 48 h.

Following the successful synthesis of tetrahydroisoquinolines 56 using the sequential one-pot method, attempts were made for the synthesis of novel 2-benzyl-2,3,4',7'-tetrahydro-1H-spiro[isoquinoline-4,3'-oxepine] systems. Notably, it was documented that the spiro-cyclic systems are useful molecules for drug discovery and show a good range of biological properties. Moreover, spiro-cyclic systems are
Table I.5: Sequential domino one-pot aza-Michael-Pd-catalyzed α-arylation for the synthesis of 1,2,3,4-tetrahydroisoquinolines 56a–56q from secondary amines 54a—54i.

explained as privileged scaffolds, since they have been successfully engaged as ligands for a wide variety of targets.\cite{53} According to our retrosynthetic analysis, it was envisioned that the targeted spiro-system 60 can be obtained from the diene 59 using a ring closing metathesis (RCM) reaction. The diene system 59 in turn could be synthesized from tetrahydroisoquinolines 56, via the LDA mediated α-allylation of 56, reduction of ester functionality followed by O-allylation sequence (Scheme I.24).
The synthetic sequence began for the synthesis of spiro tricyclics 60a and 60k with the C-allylation of α-carbon of cyclic esters 56a & 56k. The in-situ C-allylation with allyl bromide on the enolate generated by treatment of the cyclic esters 56a & 56k with lithium di-isopropyl amide (LDA), gave the products 57a & 57k (Scheme I.25).

The chemical structure of 57a was confirmed from the spectral data. The presence of the strong absorption band at 1722 and 1638 cm\(^{-1}\) due to the C=O and C=C group in the IR spectrum indicated the formation of the allyl tetrahydroisoquinoline 57a. In the \(^1\)H-NMR (Figure I.5.1) spectrum, the presence of three doublets at δ 7.35, δ 7.29 and δ 6.91 due to four aromatic protons, two doublet of doublets at δ 7.24 and δ 7.18 due to three aromatic protons, a multiplet in the region of δ 7.15–7.01 due to two aromatic protons, three multiplets in the region δ 5.70–5.31, δ 4.99–4.85 and δ 4.18–3.95 due to the three olefinic protons and two O-methylene protons, two singlets at δ 3.58 and 3.54 due to four protons two N-CH₂.
methylene groups, doublet at δ 3.06 and one multiplet in the region δ 2.75–2.60 due to four protons of two methylene groups attached to nitrogen and olefin and a triplet at δ 1.12 ppm due to three protons of a methyl group elucidated the structure of allyl 1,2,3,4-tetrahydroisoquinoline 57a. Among the 20 lines seen in $^{13}$C NMR (Figure I.5.2).
I.5.2) spectrum, existence of five quaternary carbon resonances at δ 174.3 as a result of one ester carbonyl, 138.3, 135.9 & 135.1 due to three aromatic carbons and 51.0 due to one aliphatic carbon, respectively, ten methines at δ 134.2, 129.1, 128.2, 127.9, 127.1, 126.6, 126.5 and 126.2 due to one olefinic and nine aromatic carbons, six methylenes at δ 118.3, 62.8, 60.9, 57.0, 56.7 and 42.7 and a methyl at δ 14.1 ppm confirmed the structure of allyl tetrahydroisoquinoline 57a. Presence of the [M+H]^+ ion peak at m/z 336.1942 [C_{22}H_{26}NO_2]^+ in the HR-MS spectrum concluded 57a formation.

Reduction of the esters 57a & 57k with lithium aluminum hydride (LiAlH₄) in dry ether as solvent at 0 °C to room temperature for 1 h, afforded the primary alcohols 58a & 58k in excellent yields (Scheme I.26).

![Scheme I.26](image)

The presence of the absorption band at 3396 cm⁻¹ because of O–H stretching and disappearance of the 1722 cm⁻¹ band (due to the C=O stretching) in the IR spectrum indicated the formation of the alcohol 58a, which was further proved by the existence of band at 1638 cm⁻¹ due to C=C stretching absorption band of the terminal olefin. In the ¹H NMR (Figure I.6.1) spectrum, the presence of a multiplet in the region δ 7.15–7.01 due to seven aromatic protons, one doublet of doublet at δ 7.05 and one doublet at δ 6.89 due to two aromatic protons, three multiplets were observed in the region δ 5.50–5.35 due to one olefinic proton, δ  3.78–3.65 for one methylene of CH₂OH group and one N-methylene, a broad singlet at δ 5.33 due to OH group, two doublets at δ 5.02 and δ 4.97 due to two protons of olefin methylene, two doublets at δ 3.51 and δ 3.23 due to two protons of N-methylene and four doublet of doublets at 2.87, 2.53, 2.42 and 2.11 for four protons of olefin
methylene and N-methylene clarified the structure of alcohol 58a. Of the 18 lines 13C NMR (Figure I.6.2) spectrum, existence of four quaternary carbon resonances at δ 137.6, 136.9, 135.6 and 41.7 was noticed due to three aromatic carbons, and one
aliphatic carbon, respectively, ten methines at δ 133.7, 129.1, 128.6, 127.6, 127.0, 126.3, 126.2 and 125.8 due to one olefinic and nine aromatic carbons and six methylenes at δ 118.0, 75.3, 63.0, 60.7, 56.6 and 40.0 confirmed the structure of alcohol 58a. Presence of the [M+H]+ ion peak at m/z 294.1845 [C_{20}H_{24}NO]^+ in the HR-MS spectrum concluded 58a formation.

Now, O-allylation of the hydroxyl group of alcohols 58a & 58k with allyl bromide in the presence of base NaH, furnished the corresponding allyl ethers 59a & 59k in very good yields (Scheme I.27).

![Scheme I.27](image)

The lack of the absorption band at 3396 cm⁻¹ and occurrence of a band at 1639 cm⁻¹ due to C=C in the IR spectrum showed the formation of the ether 59a. In the ¹H NMR (Figure I.7.1) spectrum, presence of five multiplets in the regions δ 7.45–7.20 due to six aromatic protons, δ 5.95–5.75, 5.65–5.50 for two methine protons of olefin & δ 3.95–3.84 and δ 3.72–3.56 because of 6 protons of three methylene groups, five doublet of doublets at δ 7.15 and δ 7.15 due to two aromatic protons & δ 3.45, 2.62 and δ 2.53 due to four methylene protons of olefin methylene and seven doublets at δ 6.96 due to one aromatic proton, δ 5.19, 5.10, 4.96, 4.91, 2.82 and 2.46 for four geminal protons of two olefin methylene groups and two protons of a methylene clarified the structure of ether 59a. Amongst the 18 lines ¹³C NMR (Figure I.7.2) spectrum, presence of four quaternary carbon resonances at δ 138.8, 138.5 & 135.8 found due to three aromatic carbons, and 42.9 is because of one aliphatic carbon, respectively, eleven methines at δ 135.3, 135.2,
128.9, 128.2, 127.2, 127.0, 126.5, 126.0 and 125.9 due to two olefinic and nine aromatic carbons.

Figure I.7.1: $^1$H-NMR (400 MHz) spectrum of 59a in CDCl$_3$

Figure I.7.2: $^{13}$C NMR (100 MHz) spectrum of 59a in CDCl$_3$
eight methylenes at $\delta$ 117.1, 116.3, 76.6, 72.3, 62.9, 57.2, 56.7 and 40.8 confirmed the structure of ether $59a$. Presence of the [M+H]$^+$ ion peak at m/z 334.2150 for [C$_{23}$H$_{28}$NO]$^+$ in the HR-MS spectrum concluded $59a$ formation.

Finally, ring closing metathesis (RCM) of the dienes $59a$ and $59k$ with 5 mol% of the first generation Grubb’s catalyst in dichloromethane at room temperature afforded the target spiro-tricyclic system $60a$ & $60k$, in very good yields, respectively (Scheme I.28).

![Scheme I.28](image)

The presence of a stretching frequency at 1603 cm$^{-1}$ due to C=C in the IR spectrum showed the formation of the spiro-oxepine $60a$. In the $^1$H NMR (Figure I.8.1) spectrum, presence of three doublet of doublets at $\delta$ 7.47, 7.31 and 7.16 due to four aromatic protons, nine doublets at $\delta$ 7.38, 6.95 (for three aromatic protons), 4.00, 3.77, 3.76, 3.56, 3.55, 3.50 and 2.69 (due to six methylene protons), a triplet at $\delta$ 7.25 and a doublet of doublet of doublet at $\delta$ 7.10 due to two aromatic protons and four multiplets in the regions $\delta$ 5.77–5.64, 5.63–5.50 (for two protons of olefin), $\delta$ 4.38–4.20 and $\delta$ 2.63–2.44 (of four methylene protons) clarified the structure of ether $60a$. In the 18 lines $^{13}$C NMR (Figure I.8.2) spectrum, presence of four quaternary carbon resonances at $\delta$ 141.4, 138.6 & 134.7 found due to three aromatic carbons, and 44.9 due to one aliphatic carbon, respectively, eleven methine carbons at $\delta$ 129.4, 128.9, 128.2, 128.0, 126.7, 126.6, 126.3 and 126.0 due to two olefinic and nine aromatic carbons and six methylene carbons at $\delta$ 78.9, 71.7, 62.8, 58.7, 56.7 and 37.1 confirmed the structure of spiro-oxepine $60a$. The presence of the
[M+Na]+ ion peak at m/z 328.1686 [C_{21}H_{23}NNaO]^+ in the HR-MS spectrum concluded 60a formation.

Figure I.8.1: $^1$H-NMR (400 MHz) spectrum of 60a in CDCl$_3$

Figure I.8.2: $^{13}$C NMR (100 MHz) spectrum of 60a in CDCl$_3$
1.4 CONCLUSIONS:

In summary, an efficient step-wise synthetic strategy for the synthesis of functionalized 1,2,3,4-tetrahydroisoquinolines was developed based on a Buchwald-Hartwig α-arylation as the key step starting from 2-bromobenzaldehydes. The method was improvised by conducting a sequential one-pot intermolecular aza-Michael addition and Pd-catalyzed intermolecular Buchwald-Hartwig α-arylation of secondary amines. An optimized neat method (only with amine & acrylate and with out any base or solvent) was established for an intermolecular aza-Michael addition to generate β-aminoesters, which were directly subjected for further intramolecular Buchwald-Hartwig α-arylation. The strategy was very efficient and amenable for the synthesis of a number of tetrahydroisoquinoline derivatives, a structural unit present in many tetrahydroisoquinoline based biologically active alkaloid natural products. Moreover, the sequential domino one-pot protocol was successfully applied for the synthesis of novel 2-benzyl-2,3,4',7'-tetrahydro-1H-spiro[isoquinoline-4,3'-oxepine] systems.

Step wise synthesis of tetrahydroisoquinolines
Domino sequential one-pot synthesis of tetrahydroisoquinolines and application to the spiro-tricyclic systems

IR spectra were recorded on Bruker Tensor 37 (FTIR) and Bruker ALPHA (FTIR) spectrophotometers. $^1$H-NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in CDCl$_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ$_H$ = 0.00 ppm) or CHCl$_3$ (δ$_H$ = 7.25 ppm). $^{13}$C-NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at RT in CDCl$_3$; chemical shifts (δ ppm) are reported relative to CHCl$_3$ [δ$_C$ = 77.00 ppm (central line of triplet)]. In the $^{13}$C-NMR, the nature of carbons (C, CH, CH$_2$ and CH$_3$) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH$_2$) and q = quartet (for CH$_3$). In the $^1$H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by $^1$H, $^{13}$C CPD (Carbon Proton Decoupling) and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Agilent 6538 UHD Q-TOF using multimode [electron spray ionization (ESI$^+$) and atmospheric pressure chemical ionization (APCI$^+$)] source. All small scale dry reactions were carried out using Schlenk tube.
and standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under inert (argon or a nitrogen) atmosphere. Solvents such as toluene, tetrahydrofuran (THF) and diethyl ether were dried over sodium metal wire, whereas dimethylformamide (DMF) and dichloromethane (DCM) were dried over calcium hydride prior to use. Solvents like petroleum ether, ethyl acetate, dichloromethane, and methanol were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C was used. Methylamine was used as 25% CH₃NH₂ in methanol. Benzylamine (with purity 98%) and ethyl acrylate (with purity 99.5%) were purchased from Sigma-Aldrich, whereas methyl acrylate (with purity 99%) and tert-butyl acrylate (with purity 98%) were purchased from other commercial sources and used as received. All benzaldehydes (with purity 98%) in order to make corresponding 2-bromobenzaldehydes [except 2-bromobenzaldehyde, which was commercially available (with purity 98%)] were purchased from commercial sources and used as received. Acme’s silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

1.5.1 Synthesis of tetrahydroisoquinolines using step-wise strategy:

General Procedure for the Reductive Amination with Benzyl Amine, for the Preparation of Secondary Amines 54a–54g (GP-1):

To an ice cold round bottomed flask containing 2-bromobenzaldehyde 53 (1 mmol), were added methanol (15 mL) followed by benzylamine (2 mmol) and acetic acid (0.3 mL). The reaction mixture was allowed to stir at room temperature for 1 h. To this reaction mixture, was added sodium borohydride (1.5 mmol) and then the reaction mixture was stirred at 65 °C for an additional 12 h. Solvent was removed under reduced pressure, treated with aqueous NH₄Cl solution and extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the secondary amine 54 (74–93%).
General Procedure for Reductive Amination with Methyl Amine, for the Preparation of Amines 54h–54i (GP-2):

To an ice cold round bottomed flask containing 2-bromobenzaldehyde 53 (1 mmol), were added methanol (15 mL) followed by methylamine (3 mmol) [25% in methanol]. The reaction mixture was allowed to stir at that ice temperature for 1 h. To this ice cold reaction mixture, was added sodium borohydride (1.5 mmol) and then the reaction mixture was allowed to attain room temperature and stirred for an additional 3 h. Solvent was removed under reduced pressure, treated with aqueous NH₄Cl solution and extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the secondary amine 54 (74–83%).

General Procedure for aza-Michael Addition (GP-3):

To the solution of secondary amine 54 (1 mmol) in methanol (4 mL), was added ethyl acrylate (2 mmol) and the reaction mixture was refluxed for 48 h and monitored by TLC. After complete conversion of starting material to the Michael addition product 55, methanol was evaporated in vacuo. Purification of the residue on a silica gel column using petroleum ether/ethyl acetate as eluent furnished pure aza-Michael addition product 55 (84–95%).

General Procedure for Buchwald–Hartwig Cyclization (GP-4):

In an oven-dried Schlenk tube under nitrogen atmosphere were taken Pd(OAc)₂ (10 mol%), Ph₃P (20 mol%), and Cs₂CO₃ (2 mmol) in toluene (1.0 mL), and the mixture was stirred for 5 min. To this mixture was added β-amino ester 55 (1 mmol) in toluene (3.0 mL), and the reaction mixture was stirred for 24 h at 80 °C and monitored by TLC. After completion of the reaction, the reaction mixture was quenched by the addition of aqueous NH₄Cl and extracted with CH₂Cl₂ (3 × 20 mL). The organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure.
pressure. Purification of the residue by column chromatography (petroleum ether/ethyl acetate) furnished the tetrahydroisoquinoline 56 (70–87%).

The secondary amines 54a, 54c, 54d and 54e are already reported in the literature.

![Structure of 54b](image)

**N-Benzyl-N-[5-(benzyl)oxy)-2-bromobenzyl]amine 54b:**

GP-1 was carried out with 2-bromo-5-benzylxybenzaldehyde 53b (1.5 g, 5.15 mmol), benzyl amine (828 mg, 10.3 mmol), acetic acid (0.3 mL) and NaBH₄ (300 mg, 7.72 mmol) in methanol (25 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to petroleum ether/ethyl acetate, 70:30) furnished the secondary amine 54b (1.46 g, 74%) as yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), Rₓ(53b)=0.70, Rₓ(54b)=0.15, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** \( \nu_{max}=3330, 2868, 1580, 1463, 1376, 1289, 1236, 1166, 1015, 807 \text{ cm}^{-1} \).

**¹H NMR (CDCl₃, 400 MHz):** \( \delta=7.52–7.28 \) (m, 11H, Ar-H), 7.13 (d, 1H, \( J=2.6 \text{ Hz} \), Ar-H), 6.80 (dd, 1H, \( J=8.7 \text{ and } 2.9 \text{ Hz} \), Ar-H), 5.09 (s, 2H, OCH₂Ph), 3.89 (s, 2H, NCH₂), 3.84 (s, 2H, NCH₂), 2.02 (br. s, 1H, NH) ppm.

**¹³C NMR (CDCl₃, 100 MHz):** \( \delta=158.2 \) (s, Ar-C), 140.3 (s, Ar-C), 140.1 (s, Ar-C), 136.7 (s, Ar-C), 133.4 (d, Ar-CH), 128.7 (d, 2C, 2 × Ar-CH), 128.5 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 128.1 (d, Ar-CH), 127.5 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 116.8 (d, Ar-CH), 115.2 (d, Ar-CH), 114.5 (s, Ar-C), 70.2 (t, OCH₂Ph), 53.2 (t, NCH₂), 53.1 (t, NCH₂) ppm.

**HR-MS (ESI⁺):** \( m/z \) calculated for \([C_{21}H_{30}BrNNaO]⁺=[M+Na]⁺: 404.0620; found 404.0621.
N-Benzyl-N-(2-bromo-3,4,5-trimethoxybenzyl)amine (54f):

GP-1 was carried out with 2-bromo-3,4,5-trimethoxybenzaldehyde 53f (1.0 g, 3.63 mmol), benzyl amine (779 mg, 7.26 mmol), acetic acid (0.4 mL) and NaBH₄ (206.9 mg, 5.44 mmol) in methanol (25 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to petroleum ether/ethyl acetate, 70:30) furnished the secondary amine 54f (1.21 g, 91%) as yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), Rf(53f)=0.60, Rf(54f)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): ν_max=3341, 2935, 1567, 1478, 1452, 1394, 1327, 1161, 1104, 974, 923, 737, 698 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ=7.42–7.30 (m, 4H, Ar-H), 7.30–7.23 (m, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 3.91 (s, 3H, Ar-OCH₃), 3.89 (s, 3H, Ar-OCH₃), 3.86 (s, 3H, Ar-OCH₃), 3.86 (s, 2H, NCH₂), 3.83 (s, 2H, NCH₂), 1.96 (br. s, 1H, NH) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ=152.6 (s, Ar-C), 150.9 (s, Ar-C), 142.1 (s, Ar-C), 140.1 (s, Ar-C), 134.9 (s, Ar-C), 128.4 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 109.9 (s, Ar-C), 109.1 (d, Ar-CH), 61.1 (q, Ar-OCH₃), 61.0 (q, Ar-OCH₃), 56.1 (q, Ar-OCH₃), 53.4 (t, NCH₂), 53.2 (t, NCH₂) ppm.

HR-MS (ESI⁺): m/z calculated for [C₁₇H₂₀BrNNaO₃]⁺=[M+Na]⁺: 388.0519; found 388.0528.

N-(2-bromobenzyl)-N-(4-methylbenzyl)amine (54g):

GP-1 was carried out with 2-bromobenzaldehyde 53a (1.0 g, 5.40 mmol), 4-methylbenzylamine (1.31 g, 8.10 mmol), acetic acid (0.4 mL) and NaBH₄ (308.4 mg, 8.10 mmol) in methanol (25 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 70:30) furnished the
product secondary amine 54g (1.38 g, 87%) as colorless viscous liquid [TLC control (petroleum ether/ethylacetate 8:2, R_f(53a)=0.70, R_f(54g)=0.25, UV detection).

IR (neat; MIR-ATR, 4000–600 cm⁻¹): ν_max=3019, 2827, 1514, 1440, 1358, 1101, 1043, 1023, 802, 747, 656 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ=7.57 (d, 1H, J=7.9 Hz, Ar-H), 7.43 (d, 1H, J=7.6 Hz, Ar-H), 7.33–7.20 (m, 3H, Ar-H), 7.17–7.07 (m, 3H, Ar-H), 3.90 (s, 2H, NCH₂), 3.79 (s, 2H, NCH₂), 2.37 (s, 3H, ArCH₃), 1.96 (br. s, 1H, NH) ppm.

13C NMR (CDCl₃, 100 MHz): δ=139.2 (s, Ar-C), 137.0 (s, Ar-C), 136.6 (s, Ar-C), 132.8 (d, Ar-CH), 130.4 (d, Ar-CH), 129.1 (d, 2C, 2 × Ar-CH), 128.6 (d, Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.4 (d, Ar-CH), 124.1 (s, Ar-C), 53.1 (t, NCH₂), 52.8 (t, NCH₂), 21.16 (q, ArCH₃) ppm.

HR-MS (ESI⁺): m/z calculated for [C₁₅H₁₇BrN]⁺=[M+H]⁺: 290.0539; found 290.0553.

Ethyl N-benzyl-N-(2-bromobenzyl)-β-alaninate (55a):

GP-3 was carried out with the secondary amine 54a (1.1 g, 3.98 mmol) and ethyl acrylate (797.9 g, 7.97 mmol) in methanol (25 mL). After completion, the reaction mixture was concentrated on the rotary evaporator and purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 99:1 to 96:4) furnished the Michael addition product ester 55a (1.32 g, 88%) as colorless liquid [TLC control (petroleum ether/ethyl acetate 9:1, R_f(54a)=0.25, R_f(55a)=0.55, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): ν_max=2980, 2805, 1731, 1444, 1368, 1244, 1182, 1129, 1024, 749, 698 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ=7.57 (d, 1H, J=7.6 Hz, Ar-H), 7.51 (d, 1H, J=8.0 Hz, Ar-H), 7.40–7.20 (m, 6H, Ar-H), 7.09 (dd, 1H, J=7.8 and 7.6 Hz, Ar-H), 4.09 (q, 2H, J=7.2 Hz, OCH₂CH₃), 3.71 (s, 2H, NCH₂), 3.64 (s, 2H, NCH₂), 2.86 (t,
2H, J=7.2 Hz, NCH₂CH₂COOEt), 2.53 (t, 2H, J=7.2 Hz, CH₂COOEt), 1.21 (t, 3H, J=7.2 Hz, OCH₂CH₃) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ=172.5 (s, O–C=O), 139.1 (s, Ar-C), 138.5 (s, Ar-C), 132.6 (d, Ar-CH), 130.6 (d, Ar-CH), 128.8 (d, 2C, 2 × Ar-CH), 128.3 (d, Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.3 (d, Ar-CH), 127.0 (d, Ar-CH), 124.3 (s, Ar-C), 60.4 (t, OCH₂CH₃), 58.3 (t, NCH₂), 57.5 (t, NCH₂), 49.4 (t, NCH₂CH₂COOEt), 32.7 (t, CH₂COOEt), 14.2 (q, OCH₂CH₃) ppm.

HR-MS (ESI⁺): m/z calculated for [C₁₉H₂₂BrNNaO₂]⁺=[M+Na]⁺: 398.0726; found 398.0729.

Ethyl N-benzyl-N-[5-(benzyloxy)-2-bromobenzyl]-β-alaninate (55b):

GP-3 was carried out with the secondary amine 54b (1.4 g, 3.66 mmol), ethylacrylate (733 mg, 7.3 mmol) in methanol (10 mL). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 85:15) furnished the β-amino ester 55b (1.6 g, 90%) as a liquid [TLC control (petroleum ether/ethyl acetate 8:2, Rf(54b)=0.20, Rf(55b)=0.55, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νmax=2980, 2933, 2815, 1732, 1591, 1463, 1373, 1275, 1237, 1183, 1018, 808 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ=7.50–7.23 (m, 12H, Ar-H), 6.75 (dd, 1H, J=8.7 and 2.8 Hz, Ar-H), 5.08 (s, 2H, OCH₂Ph), 4.12 (q, 2H, J=7.1 Hz, OCH₂CH₃), 3.68 (s, 2H, NCH₂), 3.67 (s, 2H, NCH₂), 2.88 (t, 2H, J=7.2 Hz, NCH₂CH₂COOEt), 2.53 (t, 2H, J=7.2 Hz, NCH₂CH₂COOEt), 1.23 (t, 3H, J=7.1 Hz, OCH₂CH₃) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ=172.5 (s, O–C=O), 158.2 (s, Ar-C), 139.7 (s, Ar-C), 139.1 (s, Ar-C), 136.8 (s, Ar-C), 133.1 (d, Ar-CH), 128.7 (d, 2C, 2 × Ar-CH), 128.6 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 128.1 (d, Ar-CH), 127.5 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 116.6 (d, Ar-CH), 115.3 (d, Ar-CH), 114.7 (s, Ar-C), 70.1 (t, OCH₂Ph), 60.4 (t, OCH₂CH₃), 58.3 (t, NCH₂), 57.5 (t, NCH₂), 49.6 (t, NCH₂CH₂COOEt), 32.7 (t, NCH₂CH₂COOEt), 14.2 (q, OCH₂CH₃) ppm.
HR-MS (ESI⁺): m/z calculated for [C_{29}H_{28}BrNNaO_{3}]⁺=[M+Na]⁺: 504.1145; found 504.1150.

**Ethyl N-benzyl-N-(2-bromo-5-methoxybenzyl)-β-alaninate (55c):**

GP-3 was carried out with the secondary amine 54c (4.0 g, 13.1 mmol), ethyl acrylate (2.62 g, 26.2 mmol) in methanol (40 mL) and the reaction mixture was refluxed for 2 days. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) yielded bromoester 55c (5.2 g, 98%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 6:4, R\(_f\)(54c)=0.45, R\(_f\)(55c)=0.70, UV detection)].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \(\nu_{max}=2935, 2836, 1733, 1595, 1468, 1370, 1272, 1186, 1048, 1021, 809\) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta=7.45–7.18\) (m, 7H, Ar-H), 6.68 (dd, 1H, \(J=8.7\) and 3.0 Hz, Ar-H), 4.11 (q, 2H, \(J=7.1\) Hz, OCH\(_2\)CH\(_3\)), 3.81 (s, 3H, ArOC\(_2\)H\(_3\)), 3.68 (s, 2H, NCH\(_2\)), 3.66 (s, 2H, NCH\(_2\)), 2.89 (t, 2H, \(J=7.2\) Hz, NCH\(_2\)CH\(_2\)COOEt), 2.54 (t, 2H, \(J=7.2\) Hz, NCH\(_2\)CH\(_2\)COOEt), 1.22 (t, 3H, \(J=7.1\) Hz, OCH\(_2\)CH\(_3\)) ppm.

\(^1^3\)C NMR (CDCl\(_3\), 100 MHz): \(\delta=172.5\) (s, O–C=O), 159.0 (s, Ar-C), 139.6 (s, Ar-C), 139.1 (s, Ar-C), 133.0 (d, Ar-CH), 128.7 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.0 (d, Ar-CH), 115.8 (d, Ar-CH), 114.4 (s, Ar-C), 114.2 (d, Ar-CH), 60.4 (t, OCH\(_2\)CH\(_3\)), 58.3 (t, NCH\(_2\)), 57.5 (t, NCH\(_2\)), 55.4 (q, Ar-OCH\(_3\)), 49.6 (t, NCH\(_2\)CH\(_2\)COOEt), 32.8 (t, NCH\(_2\)CH\(_2\)COOEt), 14.2 (q, OCH\(_2\)CH\(_3\)) ppm.

HR-MS (ESI⁺): m/z calculated for [C\(_{29}\)H\(_{24}\)BrNNaO\(_3\)]⁺=[M+Na]⁺: 428.0832; found 428.0833.
Ethyl N-benzyl-N-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-β-alaninate (55d):

GP-3 was carried out with the secondary amine 54d (500 mg, 1.56 mmol), ethyl acrylate (312 mg, 3.13 mmol) in methanol (20 mL). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the product ester 55d (613 mg, 93%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, \( R_f(54d)=0.30, R_f(55d)=0.55 \), UV detection)].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \( \nu_{max}=2978, 2903, 1732, 1473, 1236, 1185, 1115, 1038, 934, 838 \) cm\(^{-1}\).

\( ^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta=7.37–7.27 \) (m, 4H, Ar-H), 7.25 (dd, 1H, \( J=7.8 \) and 7.3 Hz, Ar-H), 7.10 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 5.96 (s, 2H, OCH\(_2\)O), 4.13 (q, 2H, \( J=7.1 \) Hz, OCH\(_2\)CH\(_3\)), 3.64 (s, 2H, NCH\(_2\)), 3.62 (s, 2H, NCH\(_2\)), 2.85 (t, 2H, \( J=7.1 \) Hz, NCH\(_2\)CH\(_3\)COOEt), 2.53 (t, 2H, \( J=7.1 \) Hz, NCH\(_2\)CH\(_3\)COOEt), 1.24 (t, 3H, \( J=7.1 \) Hz, OCH\(_2\)CH\(_3\)) ppm.

\( ^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta=172.5 \) (s, O–C=O), 147.4 (s, Ar-C), 147.2 (s, Ar-C), 139.1 (s, Ar-C), 131.8 (s, Ar-C), 128.8 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 114.2 (s, Ar-C), 112.4 (d, Ar-CH), 110.2 (d, Ar-CH), 101.6 (t, OCH\(_2\)O), 60.4 (t, OCH\(_2\)CH\(_3\)), 58.2 (t, NCH\(_2\)), 57.2 (t, NCH\(_2\)), 49.4 (t, NCH\(_2\)CH\(_3\)COOEt), 32.7 (t, NCH\(_2\)CH\(_3\)COOEt), 14.2 (q, OCH\(_2\)CH\(_3\)) ppm.

HR-MS (ESI\(^+\)): m/z calculated for [C\(_{20}\)H\(_{22}\)BrN\(_2\)O\(_4\)]\(^+\)=[M+Na]\(^+\): 442.0624; found 442.0638.

Ethyl N-benzyl-N-(2-bromo-4,5-dimethoxybenzyl)-β-alaninate (55e):

GP-3 was carried out with the secondary amine 54e (510 mg, 1.52 mmol), ethyl acrylate (304 mg, 3.03 mmol) in methanol (15 mL). Purification of the residue
on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the product $\beta$-aminoester 55e (629 mg, 95%) as a light brownish viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, $R_f$(54e)=0.20, $R_f$(55e)=0.50, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{\text{max}}$=2977, 2838, 1730, 1502, 1443, 1374, 1252, 1184, 1157, 1032, 799, 739, 699 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$=7.38–7.26 (m, 4H, Ar-H), 7.25–7.20 (m, 1H, Ar-H), 7.13 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 4.07 (q, 2H, $J$=7.1 Hz, OCH$_2$CH$_3$), 3.89 (s, 3H, ArOCH$_3$), 3.86 (s, 3H, ArOCH$_3$), 3.65 (s, 2H, NCH$_2$), 3.62 (s, 2H, NCH$_2$), 2.87 (t, 2H, $J$=7.1 Hz, NCH$_2$CH$_2$COOEt), 2.52 (t, 2H, $J$=7.1 Hz, CH$_2$COOEt), 1.19 (t, 3H, $J$=7.1 Hz, OCH$_2$CH$_3$) ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$=172.5 (s, O$\equiv$C=O), 148.4 (s, ArOCH$_3$), 148.3 (s, ArOCH$_3$), 139.2 (s, Ar-C), 130.6 (s, Ar-C), 128.7 (d, 2C, 2 $\times$ Ar-CH), 128.2 (d, 2C, 2 $\times$ Ar-CH), 127.0 (d, Ar-CH), 115.0 (d, Ar-CH), 113.8 (s, Ar-C), 113.1 (d, Ar-CH), 60.3 (t, OCH$_2$CH$_3$), 58.2 (t, NCH$_2$), 57.0 (t, NCH$_2$), 56.1 (q, ArOCH$_3$), 56.0 (q, ArOCH$_3$), 49.5 (t, NCH$_2$CH$_2$COOEt), 32.8 (t, CH$_2$COOEt), 14.1 (q, OCH$_2$CH$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{21}$H$_{26}$BrNNaO$_4$]$^+$_=[M+Na]$^+$: 458.0937; found 458.0937.

![Image](image-url)

**Ethyl N-benzyl-N-(2-bromo-3,4,5-trimethxybenzyl)-$\beta$-alaninate (55f):**

GP-3 was carried out with the secondary amine 54f (1.1 g, 3.27 mmol), ethyl acrylate (656 mg, 6.55 mmol) in methanol (15 mL). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 97:3 to 85:15) gave the product $\beta$-amino ester 55f (1.29 g, 92%) as a yellowish viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, $R_f$(54f)=0.30, $R_f$(55f)=0.60, UV detection)].
IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 2938, 1731, 1570, 1474, 1388, 1330, 1241, 1185, 1105, 1011, 740, 698 \text{ cm}^{-1} \).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.37 \text{–} 7.26 \text{ (m, 4H, Ar-H)}, 7.26 \text{–} 7.21 \text{ (m, 1H, Ar-H)}, 7.06 \text{ (s, 1H, Ar-H)}, 4.09 \text{ (q, 2H, } J=7.1 \text{ Hz, OCH}_2\text{CH}_3\text{)}, 3.89 \text{ (s, 3H, Ar-OCH}_3\text{)}, 3.88 \text{ (s, 6H, 2 × Ar-OCH}_3\text{)}, 3.69 \text{ (s, 2H, NCH}_2\text{)}, 3.65 \text{ (s, 2H, NCH}_2\text{)}, 2.89 \text{ (t, 2H, } J=7.1 \text{ Hz, NCH}_2\text{CH}_2\text{COOEt}), 2.54 \text{ (t, 2H, } J=7.1 \text{ Hz, CH}_2\text{COOEt}), 1.20 \text{ (t, 3H, } J=7.1 \text{ Hz, OCH}_2\text{CH}_3\text{)} \text{ ppm.}

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta = 172.5 \text{ (s, O–C=O), 152.6 \text{ (s, Ar-C), 150.5 \text{ (s, Ar-C), 141.8 \text{ (s, Ar-C), 139.1 \text{ (s, Ar-C), 134.3 \text{ (s, Ar-C), 128.6 \text{ (d, 2C, 2 × Ar-CH), 128.3 \text{ (d, 2C, 2 × Ar-CH), 127.1 \text{ (s, Ar-C), 110.0 \text{ (s, Ar-C), 108.9 \text{ (d, Ar-CH), 61.1 \text{ (q, Ar-OCH}_3\text{), 60.9 \text{ (q, Ar-OCH}_3\text{), 60.4 \text{ (t, OCH}_2\text{CH}_3\text{)}, 58.4 \text{ (t, NCH}_2\text{), 57.5 \text{ (t, NCH}_2\text{), 56.1 \text{ (q, ArOCH}_3\text{), 49.7 \text{ (t, NCH}_2\text{CH}_2\text{COOEt), 32.8 \text{ (t, CH}_2\text{COOEt), 14.2 \text{ (q, OCH}_2\text{CH}_3\text{) ppm.}}

HR-MS (ESI\(^+\)): m/z calculated for [C\(_{22}\)H\(_{28}\)BrNNaO\(_5\)]\(^+\)=[M+Na]\(^+\): 488.1043; found 488.1045.

![Ethyl N-(2-bromobenzyl)-N-(4-methylbenzyl)-β-alaninate (55g):](attachment:image.png)

Ethyl N-(2-bromobenzyl)-N-(4-methylbenzyl)-β-alaninate (55g):

GP-3 was carried out with the secondary amine 54g (600 mg, 2.07 mmol), ethyl acrylate (414 mg, 4.14 mmol) in methanol (15 mL). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 99:1 to 95:5) furnished the product β-amino ester 55g (679 mg, 84%) as colorless liquid [TLC control (petroleum ether/ethyl acetate 8:2, \( R_f(54g)=0.25, R_f(55g)=0.60, \text{ UV detection})].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 2980, 2814, 1732, 1513, 1440, 1367, 1242, 1181, 1130, 1042, 1023, 797, 749, 662 \text{ cm}^{-1} \).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.60 \text{ (d, 1H, } J=7.3 \text{ Hz, Ar-H)}, 7.50 \text{ (d, 1H, } J=7.8 \text{ Hz, Ar-H)}, 7.27 \text{ (dd, 1H, } J=7.8 \text{ and 7.8 Hz, Ar-H)}, 7.26 \text{ (d, 2H, } J=8.3 \text{ Hz, Ar-H)}, 7.08 \text{ (dd, 1H, } J=7.8 \text{ and 7.3 Hz, Ar-H}), 7.06 \text{ (d, 2H, } J=8.3 \text{ Hz, Ar-H)}, 4.14 \text{ (q,
2H, \( J=7.1 \text{ Hz}, \text{OCH}_2\text{CH}_3 \), 3.71 (s, 2H, NCH\(_2\)), 3.62 (s, 2H, NCH\(_2\)), 2.87 (t, 2H, \( J=7.2 \text{ Hz}, \text{NCH}_2\text{CH}_2\text{COOEt} \)), 2.54 (t, 2H, \( J=7.2 \text{ Hz}, \text{CH}_2\text{COOEt} \)), 2.34 (s, 3H, ArCH\(_3\)), 1.19 (t, 3H, \( J=7.1 \text{ Hz}, \text{OCH}_2\text{CH}_3 \)) ppm.

\(^{13}\text{C} \text{NMR (CDCl}_3, 100 \text{ MHz}): \delta=172.6 \text{ (s, O} \equiv \text{C-O), 138.6 \text{ (s, Ar-C), 136.6} \text{ (s, Ar-C), 135.9 \text{ (d, Ar-CH), 132.6 \text{ (d, Ar-CH), 130.6 \text{ (d, Ar-CH), 129.0 \text{ (d, 2C, 2} \times \text{Ar-CH), 128.8 \text{ (d, 2C, 2} \times \text{Ar-CH), 128.3 \text{ (d, Ar-CH), 127.3 \text{ (d, Ar-CH), 124.3 \text{ (s, Ar-C), 60.4 \text{ (t, OCH}_2\text{CH}_3 \)), 58.0 \text{ (t, NCH}_2\)), 57.4 \text{ (t, NCH}_2\)), 49.4 \text{ (t, NCH}_2\text{CH}_2\text{COOEt), 32.7 \text{ (t, CH}_2\text{COOEt), 21.1 \text{ (q, ArCH}_3\)), 14.2 \text{ (q, OCH}_2\text{CH}_3 \)) ppm.}

\text{HR-MS (ESI}^+: \text{m/z calculated for } [\text{C}_{20}\text{H}_{24}\text{BrNNaO}_2]^+=[\text{M+Na}]^+: 412.0883; \text{found } 412.0875.

Ethyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56a):

\text{GP-4 was carried out with the ester } 55a \text{ (100 mg, 0.28 mmol), Pd(OAc)}_2 \text{ (6 mg, 10 mol\%), PPh}_3 \text{ (15 mg, 20 mol\%) and Cs}_2\text{CO}_3 \text{ (182 mg, 0.56 mmol) in toluene (1.5 mL) under nitrogen atmosphere at 80 \text{ }^\circ\text{C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the tetrahydroisoquinoline 56a (64.4 mg, 82\%) as a colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 9:1, } R_f(55a)=0.55, R_f(56a)=0.45, \text{UV detection}].}

\text{IR (neat; MIR-ATR, 4000–600 cm}^{-1}: \nu_{\text{max}}=2926, 2806, 1732, 1452, 1369, 1242, 1166, 1034, 741, 699 \text{ cm}^{-1}.

\(^1\text{H} \text{NMR (CDCl}_3, 400 \text{ MHz): } \delta=7.36–7.10 \text{ (m, 8H, Ar-H), 7.06–6.98 \text{ (m, 1H, Ar-H), 4.20–4.10 \text{ (m, 2H, OCH}_2\text{CH}_3 \)), 3.85 \text{ (dd, 1H, } J=5.6 \text{ and } 4.8 \text{ Hz, CHCOOEt), 3.80 \text{ [d, 1H, } J=14.9 \text{ Hz, NCH}_2\text{(a, b)}], 3.74 \text{ [d, 1H, } J=13.2 \text{ Hz, NCH}_2\text{(a’,b’)}], 3.65 \text{ [d, 1H, } J=13.2 \text{ Hz, NCH}_2\text{(a’,b’)}], 3.59 \text{ [d, 1H, } J=14.9 \text{ Hz, NCH}_2\text{(a, b)}], 3.18 \text{ (dd, 1H, } J=11.5 \text{ and } 5.6 \text{ Hz, NCH}_2\text{CHCOOEt), 2.85 \text{ (dd, 1H, } J=11.5 \text{ and } 4.8 \text{ Hz, NCH}_2\text{CHCOOEt), 1.23 \text{ (t, 3H, } J=7.2 \text{ Hz, OCH}_2\text{CH}_3 \)) ppm.}
$^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta$=173.2 (s, O–C=O), 138.1 (s, Ar-C), 135.2 (s, Ar-C), 131.6 (s, Ar-C), 129.3 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 126.9 (d, Ar-CH), 126.7 (d, Ar-CH), 126.3 (d, Ar-CH), 62.3 (t, NCH$_2$), 60.9 (t, OCH$_2$CH$_3$), 56.1 (t, NCH$_2$), 52.9 (t, NCH$_2$CHCOOEt), 45.5 (d, CCH$_3$COOEt), 14.2 (q, OCH$_2$C$_3$H$_3$) ppm. HR-MS (ESI$^+$) m/z calculated for [C$_{19}$H$_{22}$NO$_2$]$^+=[M+H]$^+$: 296.1645; found 296.1656.

![Chemical Structure](image_url)

**Ethyl 2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinolined-4-carboxylate (56b):**

GP-4 was carried out with the ester 55b (156 mg, 0.33 mmol), Pd(OAc)$_2$ (7.2 mg, 10 mol%), PPh$_3$ (16.9 mg, 20 mol%) and Cs$_2$CO$_3$ (210 mg, 0.65 mmol) in toluene at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 85:15) furnished the tetrahydroisoquinoline 56b (105 mg, 80%) as colorless solid, m. p. 102–105 °C, recrystallized from petroleum ether and dichloromethane [TLC control (petroleum ether/ethyl acetate 8:2, $R_f$(55b)=0.60, $R_f$(56b)=0.40, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=3060, 2983, 1732, 1612, 1504, 1454, 1265, 1173, 1096, 1027, 736, 700 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$=7.50–7.25 (m, 10H, Ar-H), 7.18 (d, 1H, $J$=8.0 Hz, Ar-H), 6.87 (dd, 1H, $J$=8.0 and 2.4 Hz, Ar-H), 6.68 (d, 1H, $J$=2.4 Hz, Ar-H), 5.05 (s, 2H, OCH$_2$Ph), 4.22–4.13 (m, 2H, OCH$_2$CH$_3$), 3.88–3.53 (m, 1H, CHCOOEt), 3.83 [d, 1H, $J$=14.6 Hz, NCH$_2$(a, b)], 3.79 [d, 1H, $J$=14.6 Hz, NCH$_2$(a, b)], 3.74 [d, 1H, $J$=13.8 Hz, NCH$_2$(a’, b’)], 3.65 [d, 1H, $J$=13.8 Hz, NCH$_2$(a’, b’)], 3.21 (dd, 1H, $J$=11.4 and 5.6 Hz, NCH$_2$(CHCOOEt)), 2.90 (dd, 1H, 1H, $J$=11.4 and 4.2 Hz, NCH$_2$(CHCOOEt)), 1.24 (t, 3H, $J$=7.2 Hz, OCH$_2$CH$_3$) ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$=173.5 (s, O–C=O), 157.7 (s, Ar-C), 138.1 (s, Ar-C), 137.1 (s, Ar-C), 136.4 (s, Ar-C), 130.4 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.6 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 128.0 (d, Ar-CH), 127.5
(d, 2C, 2 × Ar-CH) 127.2 (d, Ar-CH), 124.1 (s, Ar-C), 113.6 (d, Ar-CH), 112.2 (d, Ar-CH), 70.0 (t, OCH₂Ph), 62.2 (t, OCH₂CH₃), 60.9 (t, NCH₂), 56.2 (t, NCH₂), 53.1 (t, NCH₂CHCOOEt), 44.7 (d, NCH₂CHCOOEt), 14.2 (q, OCH₂CH₃) ppm.

**HR-MS (ESI⁺):** m/z calculated for [C₂₆H₂₅NNaO₃]⁺=[M+Na]⁺: 424.1883; found 424.1887.

![Ethyl 2-benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinolin-4-carboxylate (56c):](image)

**Ethyl 2-benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinolin-4-carboxylate (56c):**

**GP-4** was carried out with the amino ester 55c (109 mg, 0.27 mmol), Pd(OAc)₂ (6 mg, 10 mol%), PPh₃ (14 mg, 20 mol%) and Cs₂CO₃ (174 mg, 0.54 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the tetrahydroisoquinoline 56c (76 mg, 87%) as a viscous liquid [TLC control (Petroleum ether/ethyl acetate 8:2, Rf (55c)=0.55, Rf (56c)=0.45, UV detection)].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** ν_{max}=2931, 2802, 1732, 1613, 1503, 1458, 1324, 1250, 1168, 1035, 854 cm⁻¹.

**¹H NMR (CDCl₃, 400 MHz):** δ=7.40–7.25 (m, 5H, Ar-H), 7.16 (d, 1H, J=8.4 Hz, Ar-H), 6.79 (dd, 1H, J=8.4 and 2.2 Hz, Ar-H), 6.58 (d, 1H, J=1.6 Hz, Ar-H), 4.24–4.10 (m, 2H, OCH₂CH₃), 3.83–3.79 (m, 1H, CHCOOEt), 3.78 (s, 3H, Ar–OCH₃), 3.77 [d, 1H, J=15.0 Hz, NCH₂(a', b')], 3.74 [d, 1H, J=13.2 Hz, NCH₂(a, b)], 3.68 [d, 1H, J=13.2 Hz, NCH₂(a, b)], 3.60 [d, 1H, J=15.0 Hz, NCH₂(a, b)], 3.19 (dd, 1H, J=11.4 and 5.7 Hz, NCH₂CH₂CHCOOEt), 2.87 (dd, 1H, J=11.5 and 4.8 Hz, NCH₂CH₂CHCOOEt), 1.23 (t, 3H, J=7.1 Hz, OCH₃CH₃) ppm.

**¹³C NMR (CDCl₃, 100 MHz):** δ=173.5 (s, O–C=O), 158.4 (s, Ar-C), 138.1 (s, Ar-C), 136.3 (s, Ar-C), 130.3 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 123.7 (s, Ar-C), 112.8 (d, Ar-CH), 111.2 (d, Ar-CH), 62.2 (t, OCH₂CH₃), 60.9 (t, NCH₂), 56.2 (t, NCH₂CHCOOEt), 55.2 (q, ArOCH₃), 53.1 (t, NCH₂), 44.6 (d, NCH₂CHCOOEt), 14.2 (q, OCH₂CH₃) ppm.
HR-MS (ESI\(^+\)): m/z calculated for \([C_{20}H_{23}NNaO_3]^+\)=[M+Na]\(^+\): 348.1570; found 348.1575.

**Ethyl 6-benzyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinolidine-8-carboxylate (56d):**

**GP-4** was carried out with the \(\beta\)-aminoester 55d (148 mg, 0.35 mmol), Pd(OAc)\(_2\) (7.9 mg, 10 mol%), PPh\(_3\) (18.4 mg, 20 mol%) and Cs\(_2\)CO\(_3\) (229 mg, 0.71 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the tetrahydroisoquinoline 56d (83 mg, 70%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 8:2, \(R_f\) (55d)=0.50, \(R_f\) (56d)=0.40, UV detection)].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)):** \(\nu_{max}=2918, 1728, 1488, 1454, 1238, 1213, 1179, 1199, 1029, 925, 730, 693 \text{ cm}^{-1}\).

**\(^1\)H NMR (CDCl\(_3\), 400 MHz):** \(\delta=7.39–7.26 \text{ (m, 5H, Ar-H)}, 6.70 \text{ (s, 1H, Ar-H)}, 6.50 \text{ (s, 1H, Ar-H)}, 5.91 \text{ (d, 2H, J=5.0 Hz, OCH}_2\text{O)}, 4.18–4.15 \text{ (m, 2H, OCH}_2\text{CH}_3\text{)}, 3.76–3.65 \text{ (m, 1H, CHCOOEt)}, 3.75 \text{ [d, 1H, J=13.0 Hz, NCH}_2\text{(a,b)}\text{]}, 3.73 \text{ [d, 1H, J=14.6 Hz, NCH}_2\text{(a',b')}\text{]}, 3.65 \text{ [d, 1H, J=13.0 Hz, NCH}_2\text{(a,b)}\text{]}, 3.51 \text{ [d, 1H, J=14.6 Hz, NCH}_2\text{(a', b')}\text{]}, 3.16 \text{ (dd, 1H, J=11.3 and 5.3 Hz, NCH}_2\text{aCHCOOEt)}, 2.82 \text{ (dd, 1H, J=11.3 and 4.1 Hz, NCH}_2\text{bCHCOOEt)}, 1.23 \text{ (t, J=7.1 Hz, 3H, OCH}_2\text{CH}_3\text{)} \text{ ppm.}\)

**\(^{13}\)C NMR (CDCl\(_3\), 100 MHz):** \(\delta=173.3 \text{ (s, O=C=O)}, 146.7 \text{ (s, Ar-C)}, 146.2 \text{ (s, Ar-C)}, 138.1 \text{ (s, Ar-C)}, 129.0 \text{ (d, 2C, 2 × Ar-CH)}, 128.6 \text{ (s, Ar-C)}, 128.3 \text{ (d, 2C, 2 × Ar-CH)}, 127.2 \text{ (d, Ar-CH)}, 124.4 \text{ (s, Ar-C)}, 109.0 \text{ (d, Ar-CH)}, 106.5 \text{ (d, Ar-CH)}, 100.9 \text{ (t, OCH}_2\text{O)}, 62.1 \text{ (t, OCH}_2\text{CH}_3\text{)}, 61.0 \text{ (t, NCH}_2\text{)}, 56.1 \text{ (t, NCH}_2\text{CHCOOEt)}, 52.8 \text{ (t, NCH}_2\text{)}, 45.3 \text{ (d, NCH}_2\text{CHCOOEt)}, 14.2 \text{ (q, OCH}_2\text{CH}_3\text{)} \text{ ppm.}\)

**HR-MS (ESI\(^+\)):** m/z calculated for \([C_{20}H_{23}NNaO_4]^+\)=[M+Na]\(^+\): 362.1363; found 362.1367.
Ethyl 2-(benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56e):

GP-4 was carried out with the bromoester 55e (100 mg, 0.23 mmol), Pd(OAc)$_2$ (5.2 mg, 10 mol%), PPh$_3$ (12.1 mg, 20 mol%) and Cs$_2$CO$_3$ (150 mg, 0.46 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 80:20) furnished the tetrahydroisoquinoline 56e (64.5 mg, 79%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, $R_f$(55e)=0.50, $R_f$(56e)=0.40, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=2931, 1729, 1514, 1455, 1366, 1252, 1134, 1032, 741, 697 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$=7.41–7.24 (m, 5H, Ar-H), 6.74 (s, 1H, Ar-H), 6.52 (s, 1H, Ar-H), 4.26–4.06 (m, 2H, OCH$_2$CH$_3$), 3.85 (s, 3H, Ar-OCH$_3$), 3.83 (s, 3H, Ar-OCH$_3$), 3.78 (dd, 1H, $J$=5.5 and 4.8 Hz, CHCOOEt), 3.74 [d, 1H, $J$=13.1 Hz, NCH$_2$(a’,b’)], 3.67 [d, 1H, $J$=14.5 Hz, NCH$_2$(a,b)], 3.65 [d, 1H, $J$=13.1 Hz, NCH$_2$(a’,b’)], 3.52 [d, 1H, $J$=14.5 Hz, NCH$_2$(a,b)], 3.17 (dd, 1H, $J$=11.4 and 5.5 Hz, NCH$_2$(CHCOOEt), 2.85 (dd, 1H, $J$=11.4 and 4.8 Hz, NCH$_2$(CHCOOEt), 1.22 (t, 3H, $J$=7.1 Hz, OCH$_2$CH$_3$) ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$=173.3 (s, O–C=O), 148.1 (s, Ar-C), 147.5 (s, Ar-C), 138.1 (s, Ar-C), 129.0 (d, 2C, 2 x Ar-CH), 128.3 (d, 2C, 2 x Ar-CH), 127.4 (s, Ar-C), 127.2 (d, Ar-CH), 123.3 (s, Ar-C), 111.8 (d, Ar-CH), 109.2 (d, Ar-CH), 62.2 (t, NCH$_2$), 60.9 (t, OCH$_2$CH$_3$), 55.9 (q, Ar-OCH$_3$), 55.8 (q, Ar-OCH$_3$), 55.7 (t, NCH$_2$), 53.0 (t, NCH$_2$(CHCOOEt), 44.9 (d, CHCOOEt), 14.2 (q, OCH$_2$CH$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{21}$H$_{23}$NNaO$_4$]$^{+}$=[M+Na]$^+$: 378.1676; found 378.1685.
Ethyl 2-benzyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolinidine-4-carboxylate (56f):

GP-4 was carried out with the β-aminoester 55f (100 mg, 0.22 mmol), Pd(OAc)$_2$ (5 mg, 10 mol%), PPh$_3$ (11.3 mg, 20 mol%) and Cs$_2$CO$_3$ (140 mg, 0.43 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 85:15) furnished the tetrahydroisoquinoline 56f (56.9 mg, 85%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, $R_f(55f)=0.55, R_f(56f)=0.45$, UV detection)] based on the recovery of starting material 55f (19 mg, 19%).

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): 2937, 1732, 1598, 1458, 1357, 1238, 1171, 1118, 1020, 741, 698 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta=7.42$–7.20 (m, 5H, Ar-H), 6.35 (s, 1H, Ar-H), 4.25–4.00 (m, 2H, OCH$_2$CH$_3$), 3.87 (s, 3H, Ar-OCH$_3$), 3.83 (s, 3H, Ar-OCH$_3$), 3.81 (s, 3H, Ar-OCH$_3$), 3.80–3.67 (m, 1H, CHCOOEt), 3.74 [d, 1H, $J=14.8$ Hz, NCH$_2$(a,b)], 3.72 [d, 1H, $J=13.2$ Hz, NCH$_2$(a’,b’)], 3.70 [d, 1H, $J=14.8$ Hz, NCH$_2$(a,b)], 3.60 [d, 1H, $J=13.2$ Hz, NCH$_2$(a’,b’)], 3.08 (dd, 1H, $J=11.5$ and 5.1 Hz, NCH$_2$(a,b)), 2.81 (dd, 1H, $J=11.5$ and 4.8 Hz, NCH$_2$(a,b)), 1.20 (t, 3H, $J=7.2$ Hz, OCH$_2$CH$_3$) ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta=173.9$ (s, O–C=O), 152.8 (s, Ar-C), 151.5 (s, Ar-C), 140.0 (s, Ar-C), 138.0 (s, Ar-C), 130.7 (s, Ar-C), 128.9 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 118.4 (s, Ar-C), 104.8 (d, Ar-CH), 62.0 (t, OCH$_2$CH$_3$), 60.7 (q, Ar-OCH$_3$), 60.7 (t, NCH$_2$), 60.3 (q, Ar-OCH$_3$), 55.9 (t and q, 2C, NCH$_2$ & ArOCH$_3$), 53.5 (t, NCH$_2$CHCOOEt), 41.3 (d, NCH$_2$CHCOOEt), 14.2 (q, OCH$_3$) ppm.

HR-MS (EST+$^+$): m/z calculated for [C$_{22}$H$_{27}$NNaO$_5$]$^+$=[M+Na]$^+$: 408.1781; found 408.1781.
Ethyl 2-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (56g):

**GP-4** was carried out with the β-aminoester 55g (100 mg, 0.26 mmol), Pd(OAc)$_2$ (5.7 mg, 10 mol%), PPh$_3$ (13.4 mg, 20 mol%) and Cs$_2$CO$_3$ (167 mg, 0.52 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the cyclic ester 56g (58.6 mg, 74%) as a colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 9:1, R$_f$(55g)=0.55, R$_f$(56g)=0.45, UV detection)].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** 2979, 2798, 1731, 1514, 1453, 1366, 1238, 1193, 1158, 1092, 1023, 803, 745, 725 cm$^{-1}$.

**$^1$H NMR (CDCl$_3$, 400 MHz):** $\delta$=7.34–7.10 (m, 7H, Ar-H), 7.06 (dd, 1H, J=8.6 and 2.8 Hz, Ar-H), 4.30–4.05 (m, 2H, OCH$_2$CH$_3$), 3.88 (dd, 1H, J=5.8 and 4.9 Hz, CHCOOEt), 3.78 [d, 1H, J=15.0 Hz, NCH$_2$(a,b)], 3.71 [d, 1H, J=13.0 Hz, NCH$_2$(a’,b’)], 3.65 [d, 1H, J=13.0 Hz, NCH$_2$(a’,b’)], 3.60 [d, 1H, J=15.0 Hz, NCH$_2$(a,b)], 3.18 (dd, 1H, J=11.4 and 5.8 Hz, NCH$_2$CHCOOEt), 2.88 (dd, 1H, J=11.5 and 4.9 Hz, NCH$_2$CHCOOEt), 2.37 (s, 3H, ArCH$_3$), 1.24 (t, 3H, J=7.1 Hz, OCH$_2$CH$_3$) ppm.

**$^{13}$C NMR (CDCl$_3$, 100 MHz):** $\delta$=173.2 (s, O=O), 136.8 (s, Ar-C), 135.2 (s, Ar-C), 135.0 (s, Ar-C), 131.6 (s, Ar-C), 129.2 (d, Ar-CH), 129.0 (d, 4C, 4 × Ar-CH), 126.9 (d, Ar-CH), 126.7 (d, Ar-CH), 126.3 (d, Ar-CH), 62.0 (t, OCH$_2$CH$_3$), 60.9 (t, NCH$_2$), 56.1 (t, NCH$_2$), 52.9 (t, NCH$_2$CHCOOEt), 45.5 (d, CHCOOEt), 21.2 (s, ArCH$_3$), 14.2 (q, OCH$_2$CH$_3$) ppm.

**HR-MS (ESI$^+$):** m/z calculated for [C$_{20}$H$_{23}$NNaO$_2$]$^+$=[M+Na]$^+$: 332.1621; found 332.1628.

**1.5.2 Synthesis of tetrahydroisoquinolines using sequential domino one-pot method from the secondary amines:**

The secondary amines 54a, 54c, 54d, 54e and 54h are reported in the literature.$^{[52]}$
General Procedure for Sequential One-pot Reaction, for the Synthesis of Tetrahydroisoquinoline 56 (GP-1):

To an oven dried Schlenk tube, were added secondary amine 54 (1 mmol) and alkyl (ethyl, or methyl and or tert-butyl) acrylate (5 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 110 °C in an oil bath, for 24 h (for methyl and ethyl acrylates) and for 48 h (for tert-butyl acrylate). Progress of the Michael addition was monitored by TLC till the reaction is completed. The reaction mixture was allowed to attain room temperature and excess of alkyl acrylate was removed under vacuum (10⁻² mbar). To the resultant reaction mixture at room temperature, were added Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%) and Cs₂CO₃ (2 mmol) followed by toluene (3 mL) under nitrogen atmosphere. The reaction mixture was then allowed to stir at 80 °C for 24 h (in case of 56h, 56i, 56a and 56d), 36 h (in case of 56b, 56c, 56j, 56l, 56m, 56n, 56p and 56q) and 48 h (in case of 56k and 56o) in an oil bath and the progress was monitored by TLC. The mixture was cooled to room temperature, treated with aqueous NH₄Cl solution and then extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the tetrahydroisoquinoline 56 (70–85%).

![Image of 54i]

N-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-N-methylamine (54i):

GP-2 was followed for the 2-bromopiperanal 53d (1.5 g, 6.55 mmol) with methyl amine (609 mg, 19.65 mmol) and NaBH₄ (374 mg, 9.82 mmol) in methanol (25 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 60:40 to ethyl acetate/methanol, 90:10) furnished the secondary amine 54i (1.18 g, 74%) as viscous liquid. [TLC control (ethyl acetate/methanol 90:10, Rf(53d)=0.90, Rf(54i)=0.35, UV detection].
IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 3291, 2893, 1501, 1473, 1408, 1389, 1369, 1230, 1114, 1033, 929, 859, 830, 786, 719, 673, 650 \text{ cm}^{-1} \).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 6.96 \) (s, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 5.93 (s, 2H, OCH\(_2\)O), 3.71 [s, 2H, Ar-CH\(_2\)N(H)Me], 2.50 (br. s, 1H, NH), 2.40 (s, 3H, NCH\(_3\)) ppm.

\(^13\)C NMR (CDCl\(_3\), 100 MHz): \( \delta = 147.3 \) (s, Ar-C), 147.3 (s, Ar-C), 131.7 (s, Ar-C), 114.2 (s, Ar-C), 112.6 (d, Ar-CH), 110.1 (d, Ar-CH), 101.6 (t, OCH\(_2\)O), 55.2 [t, ArCH\(_2\)N(H)Me], 35.4 (q, NCH\(_3\)) ppm.

HR-MS (APCI\(^{+}\)): m/z calculated for [C\(_9\)H\(_9\)BrNO\(_2\)]\(^{+}\)=[M–H]\(^{+}\): 241.9811; found 241.9802.

**Methyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56h):**

GP-1 was followed to the secondary amine 54a (276 mg, 1 mmol) with methyl acrylate (430 mg, 5 mmol) at 110 °C for 24 h. After removal of excess methyl acrylate, to the resultant reaction mixture at room temperature, were added Pd(OAc)\(_2\) (22.4 mg, 10 mol%), PPh\(_3\) (52.4 mg, 20 mol%) and Cs\(_2\)CO\(_3\) (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere, at room temperature and stirred at 80 °C in an oil bath, for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 90:10) furnished the tetrahydroisoquinoline 56h (211 mg, 75%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), \( R_f(54a)=0.40, R_f(56h)=0.55, \) UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 3026, 2949, 2803, 1732, 1495, 1453, 1433, 1239, 1197, 1163, 1094, 1028, 922, 740, 699 \text{ cm}^{-1} \).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.36–7.05 \) (m, 8H, Ar-H), 6.96 (dd, 1H, \( J=8.0 \) and 3.5 Hz, Ar-H), 3.79 (dd, 1H, \( J=5.5 \) and 4.8 Hz, CHCOOMe), 3.72 [d, 1H, \( J=15.0 \) Hz, NCH\(_2\)(a,b)], 3.66 [d, 1H, \( J=13.2 \) Hz, NCH\(_2\)(a’,b’)], 3.60 (s, 3H, COOCH\(_3\)), 3.58 [d, 1H, \( J=13.2 \) Hz, NCH\(_2\)(a’,b’)], 3.51 [d, 1H, \( J=15.0 \) Hz,
NCH₂(a,b)], 3.10 (dd, 1H, J=11.5 and 5.5 Hz, NCH₂CHCOOMe), 2.77 (dd, 1H, J=11.5 and 4.8 Hz, NCH₂CHCOOMe) ppm.

**¹³C NMR (CDCl₃, 100 MHz):** δ=173.6 (s, O=C=O), 137.9 (s, Ar-C), 135.1 (s, Ar-C), 131.4 (s, Ar-C), 129.3 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 126.9 (d, Ar-CH), 126.7 (d, Ar-CH), 126.3 (d, Ar-CH), 62.1 (t, NCH₂), 55.9 (t, NCH₂), 52.8 (t, NCH₂), 52.0 (q, COOCH₃), 45.4 (d, CHCOOMe) ppm.

**HR-MS (APCI⁺):** m/z calculated for [C₁₈H₂₀NO₂]⁺=[M+H]⁺: 282.1489; found 282.1498.

**Methyl 6-benzyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinoline-8-carboxylate (56i):**

GP-1 was followed to the secondary amine 54d (320 mg, 1 mmol) with methyl acrylate (430 mg, 5 mmol) at 110 °C for 24 h. After removal of excess methyl acrylate, to the resultant reaction mixture at room temperature, were added Pd(OAc)₂ (22.4 mg, 10 mol%), PPh₃ (52.4 mg, 20 mol%) and Cs₂CO₃ (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the tetrahydroisoquinoline 56i (260 mg, 80%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), Rᶠ(54d)=0.35, Rᶠ(56i)=0.45, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νmax=2950, 2922, 1736, 1503, 1485, 1454, 1391, 1240, 1206, 1163, 1118, 1039, 938, 863, 742, 700 cm⁻¹.

**¹H NMR (CDCl₃, 400 MHz):** δ=7.45–7.25 (m, 5H, Ar-H), 6.70 (s, 1H, Ar-H), 6.51 (s, 1H, Ar-H), 5.92 (d, 2H, J=4.8 Hz, OCH₂O), 3.77 (dd, 1H, J=5.5 and 4.8 Hz, CHCOOMe), 3.74 [d, 1H, J=13.2 Hz, NCH₂(a,b)], 3.73 [d, 1H, J=14.7 Hz, NCH₂(a’,b’)], 3.71 (s, 3H, COOCH₃), 3.65 [d, 1H, J=13.2 Hz, NCH₂(a,b)], 3.51 [d,
1H, J=14.7 Hz, NCH$_2$(a’,b’)], 3.16 (dd, 1H, J=11.5 and 5.5 Hz, NCH$_2$CHCOOMe), 2.81 (dd, 1H, J=11.5 and 4.8 Hz, NCH$_2$CHCOOMe) ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ=173.6 (s, O–C=O), 146.7 (s, Ar–C), 146.1 (s, Ar–C), 137.9 (s, Ar–C), 128.9 (d, 2C, 2 × Ar–CH), 128.5 (s, Ar–C), 128.3 (d, 2C, 2 × Ar–CH), 127.3 (d, Ar–CH), 124.3 (s, Ar–C), 109.0 (d, Ar–CH), 106.4 (d, Ar–CH), 100.8 (t, OCH$_2$O), 62.0 (t, NCH$_2$), 56.0 (t, NCH$_2$), 52.7 (t, NCH$_2$), 52.1 (q, COOCH$_3$), 45.2 (d, CHCOOMe) ppm.

HR-MS (mixed APCI$^+$ and ESI$^+$): m/z calculated for [C$_{19}$H$_{20}$NO$_4$]$^+=[M+H]$^+$: 326.1387; found 326.1373.

![56j](image)

_Tert-_butyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56j):

GP-5 was followed to the secondary amine 54a (276 mg, 1 mmol) with tert-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess tert-butyl acrylate, to the resultant reaction mixture at room temperature, were added Pd(OAc)$_2$ (22.4 mg, 10 mol%), PPh$_3$ (52.4 mg, 20 mol%) and Cs$_2$CO$_3$ (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 85:15) furnished the tetrahydroisoquinoline 56j (271 mg, 84%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R$_f$(54a)=0.35, R$_f$(56j)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=2976, 2930, 2803, 1725, 1453, 1366, 1254, 1156, 1131, 1025, 977, 846, 750, 698 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): δ=7.30 (d, 2H, J=7.3 Hz, Ar–H), 7.24 (dd, 2H, J=7.5 and 7.5 Hz, Ar–H), 7.21–7.03 (m, 4H, Ar–H), 6.93 (dd, 1H, J=5.0 and 5.0 Hz, Ar–H), 3.68 (dd, 1H, J=5.8 and 4.9 Hz, CHCOO'Bu), 3.67 [d, 1H, J=14.9 Hz, NCH$_2$(a,b)], 3.62 [d, 1H, J=13.2 Hz, NCH$_2$(a’,b’)], 3.56 [d, 1H, J=13.2 Hz, NCH$_2$(a’,b’)], 3.47 [d, 1H, J=14.9 Hz, NCH$_2$(a,b)], 3.08 (dd, 1H, J=11.5 and 5.8 Hz,
NCH₂aCHCOO'Bu), 2.78 (dd, 1H, J=11.5 and 4.9 Hz, NCH₂bCHCOO'Bu), 1.34 [s, 9H, C(CH₃)₃] ppm.

**1³C NMR (CDCl₃, 100 MHz):** δ=172.3 (s, O–C=O), 138.1 (s, Ar-C), 135.0 (s, Ar-C), 131.9 (s, Ar-C), 129.2 (d, Ar-CH), 129.1 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 126.7 (d, Ar-CH), 126.6 (d, Ar-CH), 126.1 (d, Ar-CH), 80.8 [s, COOC(CH₃)₃], 62.5 (t, NCH₂), 56.1 (t, NCH₂), 53.3 (t, NCH₂), 46.1 (d, CHCOO'Bu), 28.0 [q, 3C, C(CH₃)₃] ppm.

**HR-MS (APCI⁺):** m/z calculated for [C₂₁H₂₆NO₂⁺]=[M+H]⁺: 324.1958; found 324.1968.

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**Tert-butyl 2-benzyl-7-(benzylxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56k):**

GP-5 was followed to the secondary amine 54b (382 mg, 1 mmol) with tert-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess tert-butyl acrylate, to the resultant reaction mixture at room temperature, were added Pd(OAc)₂ (22.4 mg, 10 mol%), PPh₃ (52.4 mg, 20 mol%) and Cs₂CO₃ (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 48 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the tetrahydroisoquinoline 56k (339 mg, 79%) as pale yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 85:15), Rₛ(54b)=0.35, Rₛ(56k)=0.55, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νₘₐₓ=2976, 2798, 1724, 1611, 1502, 1454, 1366, 1272, 1242, 1132, 1094, 1026, 849, 734, 697 cm⁻¹.

**¹H NMR (CDCl₃, 400 MHz):** δ=7.45–7.20 (m, 10H, Ar-H), 7.13 (d, 1H, J=8.5 Hz, Ar-H), 6.82 (dd, 1H, J=8.5 and 2.6 Hz, Ar-H), 6.61 (d, 1H, J=2.6 Hz, Ar-H), 4.99 (s, 2H, OCH₂Ph), 3.71 [d, 1H, J=14.9 Hz, NCH₂(a,b)], 3.68 (dd, 1H, J=5.8 and 5.0 Hz, CHCOO'Bu), 3.67 [d, 1H, J=13.2 Hz, NCH₂(a',b')], 3.62 [d, 1H, J=13.2 Hz, NCH₂(a',b')], 3.49 [d, 1H, J=14.9 Hz, NCH₂(a,b)], 3.14 (dd, 1H, J=11.5 and 5.8 Hz, NCH₂(a,b)], 3.49 [d, 1H, J=14.9 Hz, NCH₂(a,b)], 3.14 (dd, 1H, J=11.5 and 5.8 Hz, NCH₂(a,b)], 3.49 [d, 1H, J=14.9 Hz, NCH₂(a,b)], 3.14 (dd, 1H, J=11.5 and 5.8 Hz, NCH₂(a,b)], 3.49 [d, 1H, J=14.9 Hz, NCH₂(a,b)], 3.14 (dd, 1H, J=11.5 and 5.8 Hz, NCH₂(a,b)].
Hz, NCH$_2$CHCOO'Bu), 2.83 (dd, 1H, $J$=11.5 and 5.0 Hz, NCH$_2$CHCOO'Bu), 1.41 [s, 9H, C(CH$_3$)$_3$] ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$=172.5 (s, O=C-O), 157.5 (s, Ar-C), 138.1 (s, Ar-C), 137.0 (s, Ar-C), 136.3 (s, Ar-C), 130.2 (d, Ar-CH), 129.0 (d, 2C, Ar-CH), 128.5 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.8 (d, Ar-CH), 127.3 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 124.4 (s, Ar-C), 113.5 (d, Ar-CH), 112.1 (d, Ar-CH), 80.7 [s, COOC(CH$_3$)$_3$], 69.9 (t, OCH$_2$Ph), 62.3 (t, NCH$_2$), 56.2 (t, NCH$_2$), 53.4 (t, NCH$_2$), 45.3 (d, CHCOO'Bu), 28.0 [q, 3C, C(CH$_3$)$_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{28}$H$_{32}$NO$_3$]$^+=[M+H]$^+$: 430.2377; found 430.2370.

**Tert-butyl 2-benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56l):**

GP-5 was followed to the secondary amine 54c (306 mg, 1 mmol) with tert-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess tert-butyl acrylate, to the resultant reaction mixture at room temperature, were added Pd(OAc)$_2$ (22.4 mg, 10 mol%), PPh$_3$ (52.4 mg, 20 mol%) and Cs$_2$CO$_3$ (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the tetrahydroisoquinoline 56l (282 mg, 80%) as yellowish brown solid, M. P. 91–93 °C (recrystallized from DCM/Hexane). [TLC control (petroleum ether/ethyl acetate 85:15), $R_f$(54c)=0.30, $R_f$(56l)=0.55, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=2975, 2926, 1727, 1613, 1504, 1454, 1366, 1274, 1245, 1146, 1095, 1030, 850, 739, 699 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$=7.29 (d, 2H, $J$=7.1 Hz, Ar-H), 7.24 (dd, 2H, $J$=7.1 and 7.1 Hz, Ar-H), 7.18 (t, 1H, $J$=7.1 Hz, Ar-H), 7.06 (d, 1H, $J$=8.5 Hz, Ar-H), 6.67 (dd, 1H, $J$=8.5 and 2.6 Hz, Ar-H), 6.45 (d, 1H, $J$=2.6 Hz, Ar-H), 3.66 (s,
3H, Ar-OCH$_3$), 3.64 [d, 1H, J=14.8 Hz, NCH$_2$(a,b)], 3.61 (dd, 1H, J=5.9 and 4.9 Hz, CHCOO'Bu), 3.59 [d, 1H, J=13.2 Hz, NCH$_2$(a',b')], 3.42 [d, 1H, J=14.8 Hz, NCH$_2$(a,b)], 3.06 (dd, 1H, J=11.5 and 5.9 Hz, NCH$_2$(a',b')].

13C NMR (CDCl$_3$, 100 MHz): $\delta$=172.6 (s, O=C=O), 158.2 (s, Ar-C), 138.1 (s, Ar-C), 136.2 (s, Ar-C), 130.2 (d, Ar-CH), 129.0 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 124.1 (s, Ar-C), 112.7 (d, Ar-CH), 111.1 (d, Ar-CH), 80.7 [s, COOC(CH$_3$)$_3$], 62.4 (t, NCH$_2$), 56.2 (t, NCH$_2$), 55.2 (q, Ar-OCH$_3$), 53.5 (t, NCH$_2$), 45.3 (d, CHCOO'Bu), 28.0 [q, 3C, C(CH$_3$)$_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{22}$H$_{28}$NO$_3$]$^+$=[M+H]$^+$: 354.2064; found 354.2074.

Tert-butyl 6-benzyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinoline-8-carboxylate (56m):

GP-5 was followed to the secondary amine 54d (320 mg, 1 mmol) with tert-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess tert-butyl acrylate, the resultant reaction mixture at room temperature, were added Pd(OAc)$_2$ (22.4 mg, 10 mol%), PPh$_3$ (52.4 mg, 20 mol%) and Cs$_2$CO$_3$ (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetrahydroisoquinoline 56m (312 mg, 85%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), $R_f$(54d)=0.30, $R_f$(56m)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=2976, 2899, 1725, 1503, 1484, 1454, 1391, 1366, 1238, 1147, 1116, 1038, 939, 849, 734, 699 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$=7.40 (d, 2H, J=7.1 Hz, Ar-H), 7.36 (dd, 2H, J=7.1 and 7.1 Hz, Ar-H), 7.30 (t, 1H, J=7.1 Hz, Ar-H), 6.72 (s, 1H, Ar-H), 6.50 (s,
1H, Ar-H), 5.91 (d, 2H, J=6.9 Hz, OCH$_2$O), 3.73 [d, 1H, J=13.0 Hz, NCH$_2$(a,b)], 3.72 (dd, 1H, J=5.8 and 4.9 Hz, CHCOO'tBu), 3.68 [d, 1H, J=14.6 Hz, NCH$_2$(a',b')], 3.65 [d, 1H, J=13.0 Hz, NCH$_2$(a,b)], 3.47 [d, 1H, J=14.6 Hz, NCH$_2$(a',b')], 3.15 (dd, 1H, J=11.5 and 5.8 Hz, NCH$_2$CHCOO'tBu), 2.84 (dd, 1H, J=11.5 and 4.9 Hz, NCH$_2$CHCOO'tBu), 1.46 [s, 9H, C(CH$_3$)$_3$] ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$=172.4 (s, O=C=O), 146.5 (s, Ar-C), 146.0 (s, Ar-C), 138.0 (s, Ar-C), 129.0 (d, 2C, Ar-CH), 128.4 (s, Ar-C), 128.2 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 124.8 (s, Ar-C), 108.9 (d, Ar-CH), 106.3 (d, Ar-CH), 100.7 (t, OCH$_2$O), 80.8 [s, COOC(CH$_3$)$_3$], 62.3 (t, NCH$_2$), 56.1 (t, NCH$_2$), 53.2 (t, NCH$_2$), 46.0 (d, CHCOO'tBu), 28.0 [q, 3C, C(CH$_3$)$_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{22}$H$_{26}$NO$_4$]$^{+}$=[M+H]$^+$: 368.1856; found 368.1849.

**Tert-butyl 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56n):**

GP-5 was followed to the secondary amine 54e (336 mg, 1 mmol) with tert-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess tert-butyl acrylate, the resultant reaction mixture at room temperature, were added Pd(OAc)$_2$ (22.4 mg, 10 mol%), PPh$_3$ (52.4 mg, 20 mol%) and Cs$_2$CO$_3$ (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 48 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 70:30) furnished the tetrahydroisoquinoline 56n (291 mg, 76%) as brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), $R_f$(54e)=0.30, $R_f$(56n)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=2974, 2933, 1724, 1612, 1517, 1463, 1453, 1365, 1254, 1225, 1132, 1028, 992, 851, 732, 698 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$=7.34 (d, 2H, J=7.1 Hz, Ar-H), 7.29 (dd, 2H, J=7.1 and 7.1 Hz, Ar-H), 7.22 (t, 1H, J=7.1 Hz, Ar-H), 6.72 (s, 1H, Ar-H), 6.46 (s,
1H, Ar-H), 3.81 (s, 3H, Ar-OCH3), 3.77 (s, 3H, Ar-OCH3), 3.68 [d, 1H, J=13.2 Hz, NCH2(a,b)], 3.66 (dd, 1H, J=6.1 and 5.0 Hz, CHCOO'Bu), 3.64 [d, 1H, J=14.4 Hz, NCH2(a',b')], 3.62 [d, 1H, J=13.2 Hz, NCH2(a,b)], 3.47 [d, 1H, J=14.4 Hz, NCH2(a',b')], 3.15 (dd, 1H, J=11.4 and 6.1 Hz, NCCH2aCHCOO'Bu), 2.84 (dd, 1H, J=11.4 and 5.0 Hz, NCH2bCHCOO'Bu), 1.40 [s, 9H, C(CH3)3] ppm.

13C NMR (CDCl3, 100 MHz): δ=172.3 (s, O–C=O), 147.9 (s, Ar-C), 147.4 (s, Ar-C), 138.1 (s, Ar-C), 129.0 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.2 (s, Ar-C), 127.1 (d, Ar-CH), 123.7 (s, Ar-C), 111.7 (d, Ar-CH), 109.2 (d, Ar-CH), 80.7 [s, COOC(CH3)3], 62.4 (t, NCH2), 55.8 (q, Ar-OCH3), 55.7 (q, Ar-OCH3), 55.6 (t, NCH2), 53.3 (t, NCH2), 45.6 (d, CHCOO'Bu), 28.0 [q, 3C, C(CH3)3] ppm.

HR-MS (APCI+): m/z calculated for [C23H30NO4]+=[M+H]+: 384.2169; found 384.2182.

Tert-butyl 2-benzyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56o):

GP-5 was followed to the secondary amine 54f (366 mg, 1 mmol) with tert-butyl acrylate (22.4 mg, 5 mmol) at 110 °C for 48 h. After removal of excess tert-butyl acrylate, to the resultant reaction mixture at room temperature, were added Pd(OAc)2 (22.4 mg, 10 mol%), PPh3 (52.4 mg, 20 mol%) and Cs2CO3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the tetrahydroisoquinoline 56o (330 mg, 80%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), Rf(54f)=0.30, Rf(56o)=0.50, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νmax=2974, 2935, 1730, 1599, 1495, 1457, 1364, 1275, 1240, 1142, 1078, 1020, 990, 743, 698, 632 cm⁻¹.
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta=7.38$ (d, 2H, $J=7.2$ Hz, Ar-H), 7.34 (dd, 2H, $J=7.2$ and 7.2 Hz, Ar-H), 7.28 (t, 1H, $J=7.2$ Hz, Ar-H), 6.34 (s, 1H, Ar-H), 3.90 (s, 3H, Ar-OCH$_3$), 3.85 (s, 3H, Ar-OCH$_3$), 3.81 (s, 3H, Ar-OCH$_3$), 3.78 [d, 1H, $J=14.8$ Hz, NCH$_2$(a,b)], 3.76 (dd, 1H, $J=5.0$ and 4.3 Hz, CHCOO$^t$Bu), 3.73 [d, 1H, $J=13.0$ Hz, NCH$_2$(a’,b’)], 3.60 [d, 1H, $J=11.5$ and 4.3 Hz, NCH$_2$aCHCOO$^t$Bu), 2.75 (dd, 1H, $J=11.5$ and 4.3 Hz, NCH$_2$CHCOO$^t$Bu), 1.43 [s, 9H, C(CH$_3$)$_3$] ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta=172.8$ (s, O–C=O), 152.6 (s, Ar-C), 151.6 (s, Ar-C), 140.1 (s, Ar-C), 138.2 (s, Ar-C), 130.6 (s, Ar-C), 129.0 (d, 2C, Ar-CH), 128.3 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 118.7 (s, Ar-C), 104.8 (d, Ar-CH), 80.0 [s, COOC(CH$_3$)$_3$], 62.3 (t, NCH$_2$), 60.6 (q, Ar-OCH$_3$), 60.3 (q, Ar-OCH$_3$), 56.0 (t, NCH$_2$), 55.9 (q, Ar-OCH$_3$), 53.8 (t, NCH$_2$), 41.9 (d, CHCOO$^t$Bu), 28.0 [q, 3C, C(CH$_3$)$_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{24}$H$_{32}$NO$_5$]$^+$=[M+H]$^+$: 414.2276; found 414.2256.

**Tert-butyl 2-methyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56p):**

GP-2 was followed to the secondary amine 54h (200 mg, 1 mmol) with tert-butyl acrylate (640 mg, 5 mmol) at 110 °C for 36 h. After removal of excess tert-butyl acrylate, to the resultant reaction mixture at room temperature, were added Pd(OAc)$_2$ (22.4 mg, 10 mol%), PPh$_3$ (52.4 mg, 20 mol%) and Cs$_2$CO$_3$ (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 80:20 to 60:40) furnished the isoquinoline 56p (175 mg, 71%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 20:80), $R_f$(54h)=0.15, $R_f$(56p)=0.45, I$_2$ chamber detection].
IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)):\ \nu_{\text{max}}=2974, 2934, 2773, 1724, 1453, 1367, 1274, 1246, 1138, 1101, 1033, 969, 850, 745 cm\(^{-1}\).

\(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta=7.19\) (dd, 1H, \(J=4.9\) and 3.4 Hz, Ar-H), 7.10 (d, 1H, \(J=3.4\) Hz, Ar-H), 7.08 (d, 1H, \(J=3.4\) Hz, Ar-H), 6.96 (dd, 1H, \(J=4.9\) and 3.4 Hz, Ar-H), 3.74 (dd, 1H, \(J=6.5\) and 5.9 Hz, CHCOO\(^t\)Bu), 3.58 [d, 1H, \(J=14.9\) Hz, NCH\(_2\)(a,b)], 3.44 [d, 1H, \(J=14.9\) Hz, NCH\(_2\)(a,b)], 2.91 (dd, 1H, \(J=11.5\) and 5.3 Hz, NCH\(_2\)CHCOO\(^t\)Bu), 2.76 (dd, 1H, \(J=11.5\) and 5.3 Hz, NCH\(_2\)CHCOO\(^t\)Bu), 2.37 (s, 3H, NCH\(_3\)), 1.40 [s, 9H, C(CH\(_3\))\(_3\)] ppm.

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta=172.3\) (s, O=C=O), 134.9 (s, Ar-C), 131.3 (s, Ar-C), 128.9 (d, Ar-CH), 126.6 (d, Ar-CH), 126.5 (d, Ar-CH), 126.2 (d, Ar-CH), 80.9 [s, COOC(CH\(_3\))\(_3\)], 57.9 (t, NCH\(_2\)), 55.4 (t, NCH\(_2\)), 45.9 (q, NCH\(_3\)), 45.8 (d, CHCOO\(^t\)Bu), 28.0 [q, 3C, C(CH\(_3\))\(_3\)] ppm.

HR-MS (APCI\(^+\)): m/z calculated for [C\(_{15}\)H\(_{22}\)NO\(_2\)]\(^+\)=[M+H]\(^+\): 248.1645; found 248.1646.

**Tert-butyl 6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinoline-8-carboxylate (56q):**

GP-2 was followed to the secondary amine 54i (244 mg, 1 mmol) with tert-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess tert-butyl acrylate, to the resultant reaction mixture at room temperature, were added Pd(OAc)\(_2\) (22.4 mg, 10 mol%), PPh\(_3\) (52.4 mg, 20 mol%) and Cs\(_2\)CO\(_3\) (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 80:20 to 55:45) furnished the isoquinoline 56q (204 mg, 70%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 20:80), \(R_f\)(54i)=0.12, \(R_f\)(56q)=0.43, UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)):\ \nu_{\text{max}}=2974, 2935, 2789, 1725, 1504, 1483, 1390, 1367, 1250, 1238, 1145, 1125, 1035, 938, 850 cm\(^{-1}\).
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta=6.71$ (s, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 5.89 (d, 1H, $J=1.4$ Hz, OCH$_2$O), 5.87 (d, 1H, $J=1.4$ Hz, OCH$_2$O), 3.68 (dd, 1H, $J=6.4$ and 5.0 Hz, CHCOO'Bu), 3.55 [d, 1H, $J=14.7$ Hz, NCH$_2$(a,b)], 3.38 [d, 1H, $J=14.7$ Hz, NCH$_2$(a,b)], 2.91 (dd, 1H, $J=11.4$ and 6.4 Hz, NCH$_2$CHCOO'Bu), 2.76 (dd, 1H, $J=11.4$ and 5.0 Hz, NCH$_2$CHCOO'Bu), 2.41 (s, 3H, NCH$_3$), 1.46 [s, 9H, C(CH$_3$)$_3$] ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta=172.4$ (s, O−C=O), 146.4 (s, Ar-C), 146.1 (s, Ar-C), 128.4 (s, Ar-C), 124.2 (s, Ar-C), 108.7 (d, Ar-CH), 106.2 (d, Ar-CH), 100.8 (t, OCH$_2$O), 81.0 [s, COOC(CH$_3$)$_3$], 57.9 (t, NCH$_2$), 55.4 (t, NCH$_2$), 45.8 (q, NCH$_3$), 45.7 (d, CHCOO'Bu), 28.1 [q, 3C, C(CH$_3$)$_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{16}$H$_{22}$NO$_4$]$^+$=[M+H]$^+$: 292.1543; found 248.1538.

Ethyl 4-allyl-2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (57a):

To a cold (−10 °C) magnetically stirred solution of diisopropylethylamine (0.10 mL, 1.35 mmol) in dry THF (1 mL) was slowly added a solution of nBuLi (2.5 M in hexane, 0.43 mL, 1.08 mmol) and the reaction mixture was stirred for 5 min at the same temperature. To the LDA thus formed, was added drop-wise, a solution of tetrahydroisoquinoline 56a (160 mg, 0.54 mmol) in dry THF (2 mL) and the reaction mixture was stirred for 30 min., at the same temperature. The enolate was then treated with allyl bromide (0.09 mL, 1.08 mmol) and stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. The reaction mixture was treated with aqueous NH$_4$Cl solution and then extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the allylated ester 57a (140.3 mg, 77%) as a pale yellow
viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), \( R_f(56a)=0.50, \) \( R_f(57a)=0.60 \), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \( \nu_{\text{max}}=3027, 2978, 2805, 1722, 1638, 1493, 1452, 1367, 1205, 1145, 1093, 1027, 918, 736, 699 \text{ cm}\(^{-1}\).**

\[ ^1H \text{NMR (CDCl}_3, 400 MHz): \] \( \delta=7.35 \text{ (d, } 1H, J=7.3 \text{ Hz, Ar-H}), 7.29 \text{ (d, } 2H, J=7.0 \text{ Hz, Ar-H}), 7.24 \text{ (dd, } 2H, J=7.0 \text{ and } 7.0 \text{ Hz, Ar-H}), 7.18 \text{ (dd, } 1H, J=7.3 \text{ and } 7.3 \text{ Hz, Ar-H}), 7.15–7.01 \text{ (m, } 2H, \text{ Ar-H}), 6.91 \text{ (d, } 1H, J=7.0 \text{ Hz, Ar-H}), 5.70–5.31 \text{ (m, } 1H, \text{ CH}_2\text{CH=CH}_2), 4.99–4.85 \text{ (m, } 2H, \text{ CH}_2\text{CH=CH}_2), 4.18–3.95 \text{ (m, } 2H, \text{ OCH}_2\text{CH}_3), 3.58 \text{ (s, } 2H, \text{ NCH}_2), 3.54 \text{ (s, } 2H, \text{ NCH}_2), 3.06 \text{ (d, } 1H, J=11.5 \text{ Hz, NCH}_2\text{CHCOOEt}), 2.75–2.60 \text{ (m, } 3H, \text{ CH}_2\text{CH=CH}_2 \text{ and NCH}_2\text{CHCOOEt}), 1.12 \text{ (t, } 3H, J=7.1 \text{ Hz, OCH}_2\text{CH}_3) \text{ ppm.} \]

\[ ^{13}C \text{NMR (CDCl}_3, 100 MHz): \] \( \delta=174.3 \text{ (s, O} \cdot \text{C=O), 138.3 \text{ (s, Ar-C), 135.9 (s, Ar-C), 135.1 (s, Ar-C), 134.2 (d, } \text{CH}_2\text{CH=CH}_2), 129.1 \text{ (d, Ar-C), 128.2 (d, } 2C, \text{ Ar-CH), 127.9 (d, } 2C, \text{ Ar-CH), 127.1 (d, Ar-CH), 126.6 (d, Ar-CH), 126.5 (d, Ar-CH), 126.2 (d, Ar-CH), 118.3 \text{ (t, } \text{CH}_2\text{CH=CH}_2), 62.8 \text{ (t, NCH}_2), 60.9 \text{ (t, OCH}_2\text{CH}_3), 57.0 \text{ (t, NCH}_2), 56.7 \text{ (t, NCH}_2), 51.0 \text{ [s, } \text{C(COOEt)}\text{CH}_2\text{CH=CH}_2\text{], 42.7 (t, } \text{CH}_2\text{CH=CH}_2) 14.1 \text{ (q, OCH}_2\text{CH}_3) \text{ ppm.} \]

**HR-MS (APCI\(^{+}\)): m/z calculated for \([C_{22}H_{26}NO_2]^+=[M+H]^+\): 336.1958; found 336.1942.**

\[ \text{Tert-butyl 4-allyl-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (57k):} \]

To a cold (–15 °C) magnetically stirred solution of diisopropylethylamine (0.16 mL, 1.51 mmol) in dry THF (1 mL) was slowly added a solution of \(^{8}\text{BuLi (2.5 M in hexane, 0.50 mL, 1.21 mmol)}\) and the reaction mixture was stirred for 5 min., at the same temperature. To the LDA thus formed, was added drop-wise, a solution of tetrahydroisoquinoline \(56k\) (260 mg, 0.61 mmol) in dry THF (2 mL) and the reaction mixture was stirred for 30 min at the same temperature. The enolate was
treated with allyl bromide (0.10 mL, 1.21 mmol) and stirred at room temperature for 4 h. The progress was monitored by TLC. The reaction mixture was treated with aqueous NH₄Cl solution and then extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 97:3 to 90:10) furnished the allylated ester 57k (221.6 mg, 78%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), Rₚ(56k)=0.45, Rₚ(57k)=0.55, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νₘₐₓ=3064, 2976, 1718, 1638, 1609, 1499, 1454, 1366, 1240, 1161, 1135, 1094, 1027, 915, 847, 734, 697 cm⁻¹.

**¹H NMR (CDCl₃, 400 MHz):** δ=7.45–7.20 (m, 11H, Ar-H), 6.82 (dd, 1H, J=8.8 and 2.9 Hz, Ar-H), 6.57 (d, 1H, J=2.9 Hz, Ar-H), 5.75–5.55 (m, 1H, CH₂CH=CH₂), 5.10–4.90 (m, 4H, CH₂CH=CH₂ and OCH₃Ph), 3.70–3.55 (m, 2H, NCH₂), 3.53 (s, 2H, NCH₂), 3.09 (d, 1H, J=11.2 Hz, NCH₂CHCOO'Bu), 2.77–2.66 (m, 3H, CH₂CH=CH₂ and NCH₂CHCOO'Bu), 1.41 [s, 9H, OC(CH₃)₃] ppm.

**¹³C NMR (CDCl₃, 100 MHz):** δ=173.5 (s, O=C=O), 157.2 (s, Ar-C), 138.4 (s, Ar-C), 137.1 (s, Ar-C), 136.4 (s, Ar-C), 134.5 (d, CH₂CH=CH₂), 129.2 (d, Ar-CH), 129.1 (d, 2C, Ar-CH), 128.8 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 118.0 (t, CH₂CH=CH₂), 113.3 (d, Ar-CH), 111.9 (d, Ar-CH), 80.8 [s, C(CH₃)₃], 69.9 (t, OCH₃Ph), 62.9 (t, NCH₂), 57.5 (t, NCH₂), 56.8 (t, NCH₂), 50.8 [s, C(CH₂O'Bu)CH₂CH=CH₂], 42.8 (t, CH₂CH=CH₂), 28.0 [q, 3C, C(CH₃)₃] ppm.

**HR-MS (APCI⁺):** m/z calculated for [C₃₁H₃₆NO₃]⁺=[M+H]⁺: 470.2690; found 470.2698.

![58a](image)

(4-Allyl-2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methanol (58a):

To a cold (−10 °C), magnetically stirred solution of the ester 57a (100 mg, 0.30 mmol) in dry diethyl ether (10 mL), was added LiAlH₄ (34 mg, 0.89 mmol).
Then the reaction mixture stirred at the same temperature for 1 h. The reaction mixture was quenched with drop wise addition of ethyl acetate then treatment with aqueous NH$_4$Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na$_2$SO$_4$), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol 58a (73.3 mg, 84%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), $R_f$(57a)=0.60, $R_f$(58a)=0.30, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{max}$=3396, 3065, 3028, 2915, 2813, 1638, 1493, 1451, 1368, 1094, 1072, 1034, 916, 755, 734, 700 cm$^{-1}$.

**$^1$H NMR (CDCl$_3$, 400 MHz):** $\delta$=7.30–7.10 (m, 7H, Ar-H), 7.05 (dd, 1H, $J$=7.5 and 7.5 Hz, Ar-H), 6.89 (d, 1H, $J$=7.5 Hz, Ar-H), 5.50–5.35 (m, 1H, CH$_2$CH=CH$_2$), 5.33 (br. s, 1H, OH), 4.92 (d, 1H, $J$=17.1 Hz, CH$_2$CH=CH$_{2\text{trans}}$), 4.88 (d, 1H, $J$=10.2 Hz, CH$_2$CH=CH$_{2\text{cis}}$), 3.78–3.65 (m, 2H, CH$_2$OH), 3.66–3.55 (m, 2H, NCH$_2$Ar), 3.51 (d, 1H, $J$=12.8 Hz, NCH$_2$Ph), 3.23 (d, 1H, $J$=12.8 Hz, NCH$_2$Ph), 2.87 [dd, 1H, $J$=11.5 and 1.6 Hz, NCH$_2$C(CH$_2$OH)CH$_2$CH=CH$_2$], 2.53 [dd, 1H, $J$=11.5 and 2.5 Hz, NCH$_2$C(CH$_2$OH)CH$_2$CH=CH$_2$], 2.42 [dd, 1H, $J$=14.4 Hz, NCH$_2$C(CH$_2$OH)CH$_2$CH=CH$_2$], 2.11 (dd, 1H, $J$=14.4 and 8.4 Hz, CH$_{2\text{trans}}$CH=CH$_2$) ppm.

**$^{13}$C NMR (CDCl$_3$, 100 MHz):** $\delta$=137.6 (s, Ar-C), 136.9 (s, Ar-C), 135.6 (s, Ar-C), 133.7 (d, CH$_2$CH=CH$_2$), 129.1 (d, 2C, Ar-CH), 128.6 (d, 2C, Ar-CH), 127.6 (d, Ar-CH), 127.0 (d, Ar-CH), 126.3 (d, Ar-CH), 126.2 (d, Ar-CH), 125.8 (d, Ar-CH), 118.0 (t, CH$_2$CH=CH$_2$), 75.3 (t, CH$_2$OH), 63.0 (t, NCH$_2$), 60.7 (t, NCH$_2$), 56.6 (t, NCH$_2$), 41.7 [s, C(CH$_2$OH)CH$_2$CH=CH$_2$], 40.0 (t, CH$_2$CH=CH$_2$) ppm.

**HR-MS (APCI$^+$):** m/z calculated for [C$_{20}$H$_{24}$NO]$^+$=[M+H]$^+$: 294.1852; found 294.1845.
[4-Allyl-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinolin-4-yl]methanol (58k):

To a cold (−10 °C), magnetically stirred solution of the ester 57k (191 mg, 0.41 mmol) in dry diethyl ether (10 mL), was added LiAlH₄ (46.4 mg, 1.22 mmol). Then the reaction mixture stirred at the same temperature for 1 h. The reaction mixture was quenched with drop-wise addition of ethyl acetate then treatment with aqueous NH₄Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol 58k (158.5 mg, 97%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 75:25), \( R_f(57k) = 0.65 \), \( R_f(58k) = 0.30 \), UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{max} = 3295, 3029, 2912, 2824, 1637, 1609, 1500, 1453, 1382, 1319, 1278, 1241, 1276, 1091, 1073, 1026, 909, 731, 697 \) cm⁻¹.

\(^1\)H NMR (CDCl₃, 400 MHz): \( \delta = 7.45–7.20 \) (m, 11H, Ar-H), 6.88 (dd, 1H, \( J = 8.8 \) and 2.9 Hz, Ar-H), 6.59 (d, 1H, \( J = 2.9 \) Hz, Ar-H), 5.65–5.40 (m, 1H, \( CH_2CH=CH_2 \)), 5.38 (br. s, 1H, OH), 5.10–4.91 (m, 4H, OCH₂Ph and \( CH_2CH=CH_2 \)), 3.85–3.55 (m, 5H, \( OCH_2Ph \) and \( NCH_2Ar \) and \( NCH_2Ph \)), 3.29 (d, 1H, \( J = 14.7 \) Hz, \( NCH_2Ph \)), 2.94 [dd, 1H, \( J = 11.7 \) and 2.0 Hz, \( NCH_2C(CH_2OH)CH_2CH=CH_2 \)], 2.53 [dd, 1H, \( J = 11.7 \) and 2.5 Hz, \( NCH_2C(CH_2OH)CH_2CH=CH_2 \)], 2.42 (dd, 1H, \( J = 14.7 \) and 6.3 Hz, \( CH_2CH=CH_2 \)), 2.11 (dd, 1H, \( J = 14.7 \) and 8.8 Hz, \( CH_2CH=CH_2 \)) ppm.

\(^13\)C NMR (CDCl₃, 100 MHz): \( \delta = 157.1 \) (s, Ar-C), 136.9 (s, Ar-C), 137.0 (s, Ar-C), 136.9 (s, Ar-C), 136.8 (s, Ar-C), 133.8 (d, \( CH_2CH=CH_2 \)), 129.9 (s, Ar-C), 129.1 (d, 2C, Ar-CH), 128.6 (d, 2C, Ar-CH), 128.5 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.6 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 126.9 (d, Ar-CH), 117.9 (t, \( CH_2CH=CH_2 \)), 114.3 (d, Ar-CH), 111.7 (d, Ar-CH), 75.2 (t, \( OCH_2Ph \)), 69.9 (t, \( CH_2OH \)), 63.0 (t, \( NCH_2 \)), 60.9 (t, \( NCH_2 \)), 56.8 (t, \( NCH_2 \)), 41.2 [s, \( C(CH_2OH)CH_2CH=CH_2 \)], 40.0 (t, \( CH_2CH=CH_2 \)) ppm.

HR-MS (APCI⁺): m/z calculated for \([C_{27}H_{28}N_2O_9]^+=[M−H]^+\): 398.2115; found 398.2104.
4-Allyl-4-[(allyloxy)methyl]-2-benzyl-1,2,3,4-tetrahydrossoquinoline (59a):

To an oven dried round bottomed flask, were added the alcohol 58a (47 mg, 0.16 mmol), sodium hydride (19 mg, 0.48 mmol) in dry DMF (3 mL) followed by addition of allyl bromide (58.2 mg, 0.48 mmol) under nitrogen atmosphere at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h and then the reaction mixture was treated with aqueous NH₄Cl solution and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the allyl ether 59a (44.2 mg, 83%) as colorless liquid. [TLC control (petroleum ether/ethyl acetate 85:15), Rf (58a)=0.35, Rf (59a)=0.75, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νmax=3064, 3027, 2924, 2853, 1639, 1493, 1452, 1368, 1345, 1145, 1090, 1027, 916, 757, 730, 698 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ=7.45–7.20 (m, 6H, Ar-H), 7.15 (dd, 1H, J=7.2 and 7.2 Hz, Ar-H), 7.10 (dd, 1H, J=7.4 and 7.4 Hz, Ar-H), 6.96 (d, 1H, J=7.4 Hz, Ar-H), 5.95–5.75 (m, 1H, CH₂CH=CH₂), 5.65–5.50 (m, 1H, CH₂CH=CH₂), 5.19 (d, 1H, J=17.2 Hz, CH₂CH=CH₂), 5.10 (d, 1H, J=10.4 Hz, CH₂CH=CH₂), 4.96 (d, 1H, J=17.4 Hz, CH₂CH=CH₂), 4.91 (d, 1H, J=10.4 Hz, CH₂CH=CH₂), 3.95–3.84 (m, 2H, CH₂OCH₂CH=CH₂), 3.72–3.56 (m, 4H, CH₂OCH₂CH=CH₂ and NCH₂Ar), 3.45 (dd, 2H, J=16.6 and 9.4 Hz, NCH₂Ph), 2.82 (d, 1H, J=11.4 Hz, CH₂CH=CH₂), 2.62 [dd, 1H, J=14.3 and 6.4 Hz, NCH₂aC(CH₂OCH₂CH=CH₂)CH₂CH=CH₂, 2.53 [dd, 1H, J=14.3 and 7.9 Hz, NCH₂aC(CH₂OCH₂CH=CH₂)CH₂CH=CH₂], 2.46 (d, 1H, J=11.5 Hz, CH₂bCH=CH₂) ppm.

13C NMR (CDCl₃, 100 MHz): δ=138.8 (s, Ar-C), 138.5 (s, Ar-C), 135.8 (s, Ar-C), 135.3 (d, CH₂CH=CH₂), 135.2 (d, CH₂CH=CH₂), 128.9 (d, 2C, Ar-CH),
128.2 (d, 2C, Ar-CH), 127.2 (d, Ar-CH), 127.0 (d, Ar-CH), 126.5 (d, Ar-CH), 126.0 (d, Ar-CH), 125.9 (d, Ar-CH), 117.1 (t, CH2CH=CH2), 116.3 (t, CH2CH=CH2), 76.6 (t, OCH2CH=CH2), 72.3 (t, CH2OCH2CH=CH2), 62.9 (t, NCH2), 57.2 (t, NCH2), 56.7 (t, NCH2), 42.9 [s, C(CH2OCH2CH=CH2)CH2CH=CH2], 40.8 (t, CH2CH=CH2) ppm.

**HR-MS (APCI+):** m/z calculated for [C23H28NO]+=[M+H]+: 334.2165; found 334.2150.

4-**Allyl-4-[(allyloxy)methyl]-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (59k):**

To an oven dried round bottomed flask, were added the alcohol 58k (132.0 mg, 0.33 mmol), sodium hydride (23.8 mg, 0.99 mmol) in dry DMF (3 mL) followed by addition of allyl bromide (120.1 mg, 0.99 mmol) under nitrogen atmosphere at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h and then the reaction mixture was treated with aqueous NH4Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with saturated NaCl solution, dried (Na2SO4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the allyl ether 59k (130.8 mg, 90%) as colorless liquid. [TLC control (petroleum ether/ethyl acetate 75:25), Rf(58k)=0.30, Rf(59k)=0.75, I2 chamber detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** 𝜈max=3064, 3029, 2851, 1637, 1609, 1578, 1499, 1453, 1342, 1278, 1240, 1139, 1091, 1019, 915, 843, 735, 697 cm⁻¹.

**1H NMR (CDCl3, 400 MHz):** δ=7.50–7.20 (m, 11H, Ar-H), 6.80 (dd, 1H, J=8.8 and 2.4 Hz, Ar-H), 6.59 (d, 1H, J=2.4 Hz, Ar-H), 5.90–5.75 (m, 1H, CH2CH=CH2), 5.70–5.50 (m, 1H, CH2CH=CH2), 5.20 (d, 1H, J=17.2 Hz,
CH₂CH=CH₂)(trans), 5.11 (d, 1H, J=10.4 Hz, CH₂CH=CH₂cis), 4.98 (s, 2H, OCH₂Ph), 5.00–4.90 (m, 2H, CH₂CH=CH₂), 3.95–3.84 (m, 2H, CH₂OCH₂CH=CH₂), 3.70–3.55 (m, 4H, CH₂OCH₂CH=CH₂ and NCH₂Ar), 3.41 (dd, 2H, J=16.6 and 9.3 Hz, NCH₂Ph), 2.79 (d, 1H, J=11.7 Hz, CH₂CH=CH₂), 2.59 [dd, 1H, J=14.2 and 6.4 Hz, NCH₂aC(CH₂OCH₂CH=CH₂)CH₂CH=CH₂], 2.50 [dd, 1H, J=14.2 and 7.8 Hz, NCH₂aC(CH₂OCH₂CH=CH₂)CH₂CH=CH₂], 2.46 (d, 1H, J=11.2 Hz, CH₂bCH=CH₂) ppm.

13C NMR (CDCl₃, 100 MHz): δ=156.9 (s, Ar-C), 138.8 (s, Ar-C), 137.2 (s, Ar-C), 137.1 (s, Ar-C), 135.4 (d, CH₂CH=CH₂), 135.2 (d, CH₂CH=CH₂), 130.9 (s, Ar-C), 128.9 (d, 2C, Ar-CH), 128.5 (d, 2C, Ar-CH), 128.3 (d, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 127.0 (d, Ar-CH), 117.1 (t, CH₂CH=CH₂), 116.3 (t, CH₂CH=CH₂), 113.2 (d, Ar-CH), 111.9 (d, Ar-CH), 76.6 (t, OCH₂CH=CH₂), 72.2 (t, CH₂OCH₂CH=CH₂), 69.9 (t, OCH₂Ph), 62.8 (t, NCH₂), 57.4 (t, NCH₂), 56.8 (t, NCH₂), 42.3 [s, C(CH₂OCH₂CH=CH₂)CH₂CH=CH₂], 40.8 (t, CH₂CH=CH₂) ppm.

HR-MS (APCI⁺): m/z calculated for [C₃₀H₃₄NO₂]⁺=[M+H]⁺: 440.2584; found 440.2581.

2-Benzyl-2,3,4',7'-tetrahydro-1H-spiro[isoquinoline-4,3'-oxepine] (60a):

To an oven dried round bottomed flask, were added the allyl ether 59a (29 mg, 0.09 mmol), Grubb’s 1st generation catalyst (3.6 mg, 5 mol%), followed by addition of DCM (7 mL) under nitrogen atmosphere at room temperature (room temperature usually is in the range of 35 to 40 °C for the hot summer, in India), stirred at room temperature for 10 h and progress was monitored by TLC. Then the reaction mixture was treated with aqueous NH₄Cl solution and extracted with DCM (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum
ether/ethyl acetate) furnished the oxepine 60a (22 mg, 82%) as colorless liquid. [TLC control (petroleum ether/ethyl acetate 95:5), \( R_f(59a) = 0.50 \), \( R_f(60a) = 0.45 \), I_2 chamber detection].

**IR** (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \( \nu_{\text{max}} = 3061, 3023, 2926, 2753, 1603, 1492, 1452, 1368, 1264, 1247, 1138, 1099, 1074, 1026, 922, 755, 732, 699 \text{ cm}^{-1} \).

\(^1\text{H NMR** (CDCl}_3, 400 \text{ MHz):} \delta = 7.47 \text{ (dd, 1H, } J = 7.8 \text{ and 1.0 Hz, Ar-H), 7.38 \text{ (d, 2H, } J = 7.3 \text{ Hz, Ar-H), 7.31 \text{ (dd, 2H, } J = 7.3 \text{ and 7.3 Hz, Ar-H), 7.25 \text{ (t, 1H, } J = 7.3 \text{ Hz, Ar-H), 7.18 \text{ (dd, 1H, } J = 7.8 \text{ and 7.8 Hz, Ar-H), 7.10 \text{ (dd, 1H, } J = 7.8 \text{, 7.8 and 1.0 Hz, Ar-H), 6.95 \text{ (d, 1H, } J = 7.8 \text{ Hz, Ar-H), 5.77–5.64} \text{ (m, 1H, } \text{CH}_a = \text{CH}_b), 5.63–5.50 \text{ (m, 1H, } \text{CH}_a = \text{CH}_b), 4.38–4.20 \text{ (m, 2H, } \text{CH}_2 \text{OCH}_2 \text{CH=CH}), 4.00 \text{ (d, 1H, } J = 12.2 \text{ Hz, } \text{CH}_2 \text{OCH}_2 \text{CH=CH}), 3.77 \text{ (d, 1H, } J = 12.2 \text{ Hz, } \text{CH}_2\text{OCH}_2\text{CH=CH}), 3.76 \text{ (d, 1H, } J = 13.2 \text{ Hz, } \text{NCH}_2 \text{Ar}), 3.56 \text{ (d, 1H, } J = 14.7 \text{ Hz, } \text{NCH}_2 \text{Ph}), 3.55 \text{ (d, 1H, } J = 13.2 \text{ Hz, } \text{NCH}_2 \text{Ar}), 3.50 \text{ (d, 1H, } J = 14.7 \text{ Hz, } \text{NCH}_2 \text{Ph}), 2.69 \text{ [d, 1H, } J = 11.7 \text{ Hz, NCH}_2 \text{C(CH}_2\text{OCH}_2\text{CH}_2\text{CH=CH}], 2.63–2.44 \text{ [m, 3H, NCH}_2\text{C(CH}_2\text{OCH}_2\text{CH}_2\text{CH=CH and CH}_2\text{CH=CH] ppm.**}

\(^{13}\text{C NMR** (CDCl}_3, 100 \text{ MHz):} \delta = 141.4 \text{ (s, Ar-C), 138.6 \text{ (s, Ar-C), 134.7 \text{ (s, Ar-C), 129.4 \text{ (d, } \text{CH}_a = \text{CH}_b), 128.9 \text{ (d, 2C, Ar-CH), 128.2 \text{ (d, 2C, Ar-CH), 128.0 \text{ (d, Ar-CH), 127.0 \text{ (d, Ar-CH), 126.7 \text{ (d, Ar-CH), 126.6 \text{ (d, Ar-CH), 126.3 \text{ (d, Ar-CH), 126.0 \text{ (d, } \text{CH}_a = \text{CH}_b), 78.9 \text{ (t, } \text{OCH}_2\text{CH=CH}), 71.7 \text{ (t, } \text{CH}_2\text{OCH}_2\text{CH=CH}), 62.8 \text{ (t, } \text{NCH}_2\text{), 58.7 \text{ (t, } \text{NCH}_2\text{), 56.7 \text{ (t, } \text{NCH}_2\text{), 44.9 \text{ [s, } \text{C(CH}_2\text{OCH}_2\text{CH}_2\text{CH=CH}], 37.1 \text{ (t, } \text{CH}_2\text{CH=CH] ppm.**}

**HR-MS** (ESI\(^+\)): m/z calculated for [C\(_{21}\)H\(_{23}\)NNaO]\(^+\)=[M+Na]\(^+\): 328.1672; found 328.1686.

2-Benzyl-7-(benzyloxy)-2,3,4',7'-tetrahydro-1H-spiro[isoquinoline-4,3'-oxepine] (60k):

To an oven dried round bottomed flask, were added the allyl ether 59k (37 mg, 0.08 mmol), Grubb’s 1\(^{st}\) generation catalyst (3.5 mg, 5 mol%), followed by
addition of DCM (6 mL) under nitrogen atmosphere at room temperature (room temperature usually is in the range of 35 to 40 °C for the hot summer, in India), stirred at room temperature for 10 h and progress was monitored by TLC. Then the reaction mixture was treated with aqueous NH₄Cl solution and extracted with DCM (3 × 15 mL). The organic layer was washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the oxepine 60k (29.0 mg, 83%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), Rₖ(59k)=0.55, Rₖ(60k)=0.45, I₂ chamber detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νₘₚₚₜ=3062, 3026, 2926, 1609, 1580, 1499, 1454, 1318, 1239, 1097, 1021, 908, 732, 697 cm⁻¹.

**¹H NMR (CDCl₃, 400 MHz):** δ=7.40–7.10 (m, 11H, Ar-H), 6.74 (d, 1H, J=8.8 and 2.9 Hz, Ar-H), 6.49 (d, 1H, J=2.9 Hz, Ar-H), 5.70–5.57 (m, 1H, CH₂=CH₂), 5.55–5.45 (m, 1H, CH₂=CH₂), 4.25–4.18 (m, 2H, CH₂OCH₂CH=CH), 3.93 (d, 1H, J=12.2 Hz, CH₂OCH₂CH=CH), 3.68 (d, 1H, J=13.2 Hz, NCH₂Ar), 3.65 (d, 1H, J=12.2 Hz, CH₂OCH₂CH=CH), 3.47 (d, 1H, J=13.2 Hz, NCH₂Ar), 3.42 (d, 1H, J=14.7 Hz, NCH₂Ar), 3.38 (d, 1H, J=14.7 Hz, NCH₂Ar), 2.62 [d, 1H, J=11.2 Hz, NCH₂C(CH₂OCH₂)CH₂CH=CH], 2.52–2.35 [m, 3H, NCH₂C(CH₂OCH₂)CH₂CH=CH and CH₂=CH] ppm.

**¹³C NMR (CDCl₃, 100 MHz):** δ=156.9 (s, Ar-C), 138.6 (s, Ar-C), 137.1 (s, Ar-C), 136.1 (s, Ar-C), 133.8 (s, Ar-C), 129.4 (d, CH₂=CH₂), 128.8 (d, 2C, Ar-CH), 128.5 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.9 (d, Ar-CH), 127.8 (d, CH₂=CH₂), 127.4 (d, 2C, Ar-CH), 127.0 (d, Ar-CH), 113.8 (d, Ar-CH), 111.6 (d, Ar-CH), 78.9 (t, OCH₂CH=CH), 71.6 (t, CH₂OCH₂CH=CH), 69.9 (t, OCH₂Ph), 62.8 (t, NCH₂), 58.8 (t, NCH₂), 44.2 [s, C(CH₂OCH₂)CH₂CH=CH], 37.2 (t, CH₂CH=CH) ppm.

**HR-MS (ESI⁺):** m/z calculated for C₂₅H₃₀NO₂⁺=[M+H]⁺: 412.2271; found 412.2279.
Figure I.9.1: $^1$H NMR (400 MHz) spectrum of 54b in CDCl$_3$

Figure I.9.2: $^{13}$C NMR (100 MHz) spectrum of 54b in CDCl$_3$
Figure I.10.1: $^1$H NMR (400 MHz) spectrum of 54e in CDCl$_3$

Figure I.10.2: $^{13}$C NMR (100 MHz) spectrum of 54e in CDCl$_3$
Figure I.11.1: $^1$H NMR (400 MHz) spectrum of 55f in CDCl$_3$

Figure I.11.2: $^{13}$C NMR (100 MHz) spectrum of 55f in CDCl$_3$
Figure I.12.1: $^1$H NMR (400 MHz) spectrum of 55h in CDCl$_3$

Figure I.12.2: $^{13}$C NMR (100 MHz) spectrum of 55h in CDCl$_3$
Figure I.13.1: $^1$H NMR (400 MHz) spectrum of 56h in CDCl$_3$

Figure I.13.2: $^{13}$C NMR (100 MHz) spectrum of 56h in CDCl$_3$
Figure I.1.1: $^1$H NMR (400 MHz) spectrum of 56j in CDCl$_3$

Figure I.1.2: $^{13}$C NMR (100 MHz) spectrum of 56j in CDCl$_3$
Figure I.15.1: $^1$H NMR (400 MHz) spectrum of $57k$ in CDCl$_3$

Figure I.15.2: $^{13}$C NMR (100 MHz) spectrum of $57k$ in CDCl$_3$
Figure I.16.1: $^1$H NMR (400 MHz) spectrum of $58k$ in CDCl$_3$

Figure I.16.2: $^{13}$C NMR (100 MHz) spectrum of $58k$ in CDCl$_3$
Figure I.17.1: $^1$H NMR (400 MHz) spectrum of $59k$ in CDCl$_3$

Figure I.17.2: $^{13}$C NMR (100 MHz) spectrum of $59k$ in CDCl$_3$
Figure I.18.1: $^1$H NMR (400 MHz) spectrum of 60k in CDCl$_3$

Figure I.18.2: $^{13}$C NMR (100 MHz) spectrum of 60k in CDCl$_3$
CHAPTER II

SYNTHESIS OF CINNAMATE DIESTERS, ISOCHROMENES AND 2-BENZOXEPINONES

II.1 INTRODUCTION:

Organic chemistry has always demanded more efficient and economical synthetic strategies in the course of building this vast subject. Synthetic strategies involving fewer steps have been of great significance in recent times. In this regard, one-pot procedures are considered helpful for the synthesis of a variety of complex organic molecules, with no intermediate isolation.[55] This kind of one-pot transformation is possible by using a single metal complex to catalyze a sequence of multiple reactions,[56] or by the sequential addition of various metal/non-metal catalysts to achieve a multiple reaction series.[57] These types of reactions are known as multi-catalytic domino cascades, pseudo domino strategies, sequential domino one-pot protocol, telescoping synthesis and tandem reactions. These processes are of immense advantage to synthetic organic chemists, as they are recognized to have numerous benefits over normal step-wise operations, like they avoid intermediate species isolation, thereby considerably reducing waste generation, increasing strategic efficiency, using solvents and reagents minimally, and most importantly,
saving time.\textsuperscript{[50]} In addition, it was also observed that in most cases, overall yields from one-pot processes were usually greater than those obtained from corresponding step-wise methods. Thus, one-pot syntheses that form multiple C–C bonds and complex cyclic structures are of immense interest and are desirable, as these complex cyclic structures constitute the core of many natural products with interesting biological activities.

In recent times, one-pot processes catalyzed by transition metals and their development have gained much attention from synthetic organic chemists due to their practical advantages and unexpected novel reactions.\textsuperscript{[58],[59]} Among a variety of these reactions, protocols involving palladium catalyzed Heck reactions were found to be the most useful and well documented.\textsuperscript{[60],[61],[62]} A few examples of this kind of reaction and other associated transformations reported by different research groups involved oxidative-Heck reaction, Michael addition, electrocyclic ring closure and C–H activation.

Very recently, Schmidt and Elizarov reported a novel sequential one-pot deacetyltative diazotization followed by Heck coupling on acetanilide esters 1 leading to the cimamate diesters 3 via the intermediate 2 (Scheme II.1).\textsuperscript{[63]}

![Scheme II.1](image)

Pfeffer et al developed the palladium-catalyzed domino Heck followed by aza-Michael addition reactions,\textsuperscript{[64]} for the synthesis of a series of isoindolines 5, tetrahydroisoquinolines 7 and tetrahydro-β-carbolines 9 from the corresponding precursors 4, 6 and 8. The domino process involved the intermolecular Heck reaction of a haloarene with a Michael acceptor followed by an intramolecular aza-cyclization (intramolecular aza-Michael addition) reaction (Scheme II.2).
The research group of Takemoto established a domino palladium catalyzed Heck cyclization, for the formation of the spiro-tricyclic indole derivative \( \text{11} \) as a major product. Whereas, the Lewis acid (bismuth triflate) catalyzed hydroamination of the simple Heck cyclized product \( \text{12} \) gave the same spiro-tricyclic system \( \text{11} \), which represents the skeleton of elacomine and isoealcomine (Scheme II.3).

A novel domino reaction carried out by Langer et al involving a tandem double Heck reaction followed by electrocyclic ring closure of 2,3-dibromo-N-methylindole \( \text{13} \), using \( \text{Pd(OAc)}_2 \) as the catalyst and a selective biaryl monophosphine ligand, resulted in dihydrocarbazoles \( \text{14} \) (Scheme II.4).
The same research group disclosed the synthesis of anthraquinones 16 and 17 from dibromonaphthaquinone 15 (Scheme II.5).\[67\]

The efforts of Trost and his co-workers\[68\] to synthesize FR900482, an epimer of anti-cancer, along with the 8-exo-trig Heck reaction to afford the benzazacine core from the precursor 18, led to domino intramolecular C–H activation and furnished 19 (Scheme II.6).

In spite of its wide applications, the popularity and reports of the Heck reaction, in combination with a succeeding cyclization step (for example, intramolecular Michael addition), are limited. It might be ideal to choose a base that would be suitable to promote both the Heck coupling as well as cyclization addition, as most of the palladium catalyzed transformations were base controlled.
reactions. Remarkably, there were fewer approaches documented on Pd-catalyzed Heck-Michael, and Heck-aza-Michael one-pot processes.

II.2 RESULTS AND DISCUSSION:

II.2.1 Sequential one-pot synthesis of cinnamate diesters and isochromenes:

After successfully obtaining functionalized 1,2,3,4-tetrahydroisoquinolines by palladium catalysis and their extension to spiro-tricyclic oxepines (Chapter I) and based on the research literature initially, the synthesis of isobenzofurans was targeted from ortho-bromobenzyl alcohols through the palladium catalyzed intermolecular Heck reaction followed by an intramolecular Michael addition reaction with Michael acceptors. It was envisioned that the use of a single base would be capable of promoting both Pd-catalysis as well as oxy-Michael addition. The requisite precursors, 2-bromobenzyl alcohols were readily obtained by simple reduction from sodium borohydride (Scheme II.7).

Thus, the synthetic study was initiated with the preparation of 2-bromobenzaldehydes. The required ortho-bromobenzyl alcohols were synthesized by the standard reduction reaction of 2-bromobenzaldehydes. Thus, treatment of 2-bromobenzaldehydes with the sodium borohydride (fractional addition for about 10 minutes to avoid vigorous effervescence) at ice-cold temperature in methanol, followed by stirring the reaction
mixture at room temperature for one hour, furnished the 2-bromobenzylprimary alcohols 21a–21h. The chemical structure of the 2-bromobenzyl alcohol 21d was confirmed from the spectral data of 21d. The lack of an absorption band due to carbonyl stretching of aldehyde group and the existence of the broad absorption
band at 3372 cm\(^{-1}\) due to the O–H stretching in the IR spectrum, indicated the formation of the 2-bromobenzyl alcohol 21d. In the \(^1\)H-NMR spectrum, the absence of aldehyde proton resonance, the presence of three doublets at \(\delta\) 7.42, 7.36 and 7.35 due to four aromatic protons, a triplet at \(\delta\) 7.29 due to one aromatic proton, two singlets at \(\delta\) 7.02 due to two aromatic protons, three singlets at \(\delta\) 5.11 and 4.59 due to four protons of two methylenes and 3.85 for one O-methyl proton and one broad singlet at \(\delta\) 2.05 ppm for the proton of hydroxyl group elucidated the structure of the 2-bromobenzyl alcohol 21d (Figure II.1.1). In addition, the appearance of five quaternary carbon resonances at \(\delta\) 149.6, 147.6, 136.6, 131.7 and 113.1 due to five aromatic carbons, seven methine carbons at \(\delta\) 128.6, 128.0, 127.4, 115.8 and 114.4, two methylenes at 71.1 and 64.7 and one quartet at 56.2 ppm in the 13 lines of \(^{13}\)C-NMR spectrum confirmed the structure of 2-bromobenzyl alcohol 35a (Figure II.1.2). On the other hand, the requisite secondary alcohols 21k–21o were achieved by the standard methyl Grignard reaction on the corresponding 2-bromobenzaldehydes 35. The reagent methylmagnesium iodide, which was used for the Grignard reaction, was prepared by the activation of a catalytic amount of magnesium by molecular iodine, followed by drop wise addition of methyl iodide to the magnesium metal in dry ether under an inert atmosphere.

To initiate the synthetic study, 2-bromobenzyl alcohol 21g was chosen as the model for the synthesis of expected isobenzofurans 22g via palladium catalyzed domino one-pot Heck followed oxy-Michael addition sequence. Thus, initially, 2-bromobenzyl alcohol 21g was treated with varying amounts of ethyl acrylate (2–5 equiv) in the presence of palladium catalyst [10 mol\% of Pd(OAc)\(_2\), 20 mol\% of PPh\(_3\)] with the base Cs\(_2\)CO\(_3\) (2 equiv) in hot toluene (or DMF) for 24 h (Scheme II.8). Unexpectedly, the result was the formation of a cinnamate derivative 23g, albeit in very poor yield (9\% by using 2 equivalents of ethyl acrylate and 29\% with 5 equivalents of ethyl acrylate) along with a reasonable amount of simple veratraldehyde 24g (54\% by using 2 equivalents of ethyl acrylate and 26\% with 5 equivalents of ethyl acrylate). The formation of 23g took place via initial intermolecular oxy-Michael addition and succeeding intermolecular Heck coupling
instead of the expected cyclic ether 22g through initial intermolecular Heck coupling followed by intramolecular oxy-Michael addition. This might be due to preferential nucleophilicity of the benzyl alcohol moiety 21g towards the Michael acceptor ethyl acrylate over the intermolecular Heck reaction (Scheme II.8).

Scheme II.8

However, the latter one 24g was formed by reductive debromination and oxidative cleavage. This can be explained by a competing formation of aryl-palladium(II) species A, which upon intramolecular coordination with neighbouring free benzylic OH group would lead to a five-membered palladacycle B. Then, subsequent cycloreversion of the pallacycle due to β-hydrogen atom transfer would lead to the benzaldehydes 24g (scheme II.9).[72]
The formation and structure of the diester 23g was apparent from the spectral data. The absence of a broad absorption band due to O–H stretching and the existence

Figure II.2.1: $^1$H NMR (400 MHz) of compound 23g in CDCl$_3$

Figure II.2.2: $^{13}$C NMR (100 MHz) of compound 23g in CDCl$_3$
of the absorption band at 3372 cm\(^{-1}\) due to the carbonyl stretching of ester group in the IR spectrum showed the formation of diester 23g. In the \(^1\)H-NMR spectrum (Figure II.2.1), absence of O–H proton resonance, the presence of two doublets at \(\delta\) 7.89 and 6.25 due to two olefinic protons, two singlets at \(\delta\) 7.05 and 6.89 due to two aromatic protons, three singlets in the aliphatic region at \(\delta\) 4.59 due to one benzylic methylene, 3.89 and 3.87 for two O-methyl groups, two quartets at \(\delta\) 4.23 and 4.11 due to four protons of two O-methylene protons and four triplets at \(\delta\) 3.77, 2.60, 1.31 and 1.25 ppm for 10 protons of two methylenes and two methyl moieties established the structure of diester 23g. Additionally, the detection of six quaternary carbon resonances at \(\delta\) 171.4 and 167.0 for two ester carbonyl carbons, signals at \(\delta\) 150.7, 148.7, 130.9 and 125.7 for the four aromatic carbons, four methine carbons at \(\delta\) 140.9 and 109.0 due to two olefinic carbons, 117.7 and 112.1 of two aromatic carbons, five methylenes at 70.2, 65.8, 60.5, 60.4 and 35.1 and four quartets at 56.0, 14.3 and 14.1 ppm from 18 lines of \(^{13}\)C-NMR spectrum (Figure II.2.2) concluded the structure of diester 23g.

Since the yield of product 23g was very poor when the reaction was performed by direct addition of both the Michael acceptor and catalyst together with the 2-bromobenzyl alcohol 21g, expected the sequential addition of the Michael acceptor (i.e. for the initial oxy-Michael addition in selective fashion) and loading of the palladium catalyst would help achieve 23g in improved yields due to the high selectivity of each individual step of the reaction sequence. Thus oxy-Michael addition was administered for optimization. The treatment of 21g with excess ethyl acrylate (5 equiv) in hot toluene (80 °C) for 48 h, furnished the expected oxy-Michael addition product, the bromoester 25g, in fair yield (58%) along with the undesired condensed ester by-product 26g in 22% yield (entry 1, Table II.1; Scheme II.10).
**Scheme II.10**

**Table II.1**: Optimization with various screening reaction conditions, for one-pot synthesis of 23g.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (2 equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield 25g (%)</th>
<th>Yield 26g (%)</th>
<th>Yield 23g (%)</th>
<th>Yield 24g (%)</th>
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<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>toluene</td>
<td>80</td>
<td>24</td>
<td>58</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>toluene</td>
<td>RT</td>
<td>72</td>
<td>73</td>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>toluene</td>
<td>50</td>
<td>48</td>
<td>78</td>
<td>16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>50</td>
<td>48</td>
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<td>-</td>
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<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>50</td>
<td>48</td>
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<td>-</td>
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<td>-</td>
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<tr>
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<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>THF</td>
<td>65</td>
<td>24</td>
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<td>-</td>
<td>-</td>
<td>10</td>
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<tr>
<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>80</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>K&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>DMF</td>
<td>80</td>
<td>20</td>
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<td>-</td>
<td>5</td>
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<tr>
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<td>DMF</td>
<td>50</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>-</td>
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</tbody>
</table>

<sup>a</sup> Isolated yields of chromatographically pure products (25g and 26g) and hence subsequent palladium catalyzed Heck coupling was not performed. <sup>b</sup> Isolated yields of products (25g and 26g) based on starting material recovery and hence subsequent palladium catalyzed Heck coupling was not performed. <sup>c</sup> No oxy-Michael addition product was isolated and
subjected to in situ palladium catalyzed Heck coupling. Isolated yields of chromatographically pure products (23g and 24g).

We presumed that the decrease in temperature might prevent the formation of by-product 26g and may improve the selectivity for the formation of bromoester 25g. Quite interestingly, the reaction at ambient temperature showed a promising incremental effect in yield (73%) of 25g at the expense of 26g (14%) based on the recovery of starting material 21g (entry 2, Table II.1). Gratifyingly, the product 25g was furnished in very good yield (78%) along with 26g (16%) at 50 °C for 48 h (entry 3, Table II.1).

The formation and structure of ester 25g was obvious from the spectral data of 25g. Absence of the broad absorption band due to O–H group and presence of absorption band at 1732 cm$^{-1}$ for the ester carbonyl stretching in the IR spectrum indicated the formation of ester 25g. In the $^1$H-NMR spectrum (Figure II.3.1), the absence of O–H proton resonance, the presence of four singlets at $\delta$ 6.98 (due to two aromatic protons), 4.52 (due to two protons of benzylic methylene group), 3.86 and 3.84 (due to six protons of two O-methyl groups), a quartet at $\delta$ 4.14 (due to two protons of O-methylene group) and three triplets at $\delta$ 3.79, 2.62 and 1.24 ppm (due to four protons of two methylene groups and for three protons of one methyl group) elucidated the structure of ester 25g. In addition, in 14 lines $^{13}$C-NMR spectrum (Figure II.3.2), presence of five quaternary carbon resonances at $\delta$ 171.5 (due to ester carbonyl), 148.8, 148.5, 129.4 and 112.7 (due to four aromatic carbons), two aromatic methine carbons at $\delta$ 115.2 and 111.9, four methylenes at 72.0, 65.9, 60.5 and 35.1, three methyls at 56.1, 56.0 and 14.2 ppm confirmed the structure of ester 25g.
In a similar way, the structure and formation of ester 26g was obvious from the spectral data of 26g. The disappearance of a broad absorption band due to O–H
Figure II.4.1: $^1$H NMR (400 MHz) of compound $26g$ in CDCl$_3$

Figure II.4.2: $^{13}$C NMR (100 MHz) of compound $26g$ in CDCl$_3$

group and existence of absorption band at 1722 cm$^{-1}$ due to ester carbonyl stretching in the IR spectrum signified the formation of ester $26g$. In the $^1$H-NMR spectrum...
(Figure II.4.1), the presence of five singlets at δ 7.03 and 6.93 (due to two aromatic protons), 5.21 (because of two protons of benzylic methylene group), 3.86 and 3.85 (for six protons of two methoxy groups), and three doublet of doublets at δ 6.45, 6.16 and 5.85 ppm (due to three protons of vinyl group) established the structure of the condensed ester 26g. To support it the 14 lines in 13C-NMR spectrum (Figure II.4.2), showed the presence of five quaternary carbon resonances at δ 165.9 (due to ester carbonyl), δ 149.6, 148.3, 127.0 and 114.4 (due to four aromatic carbons), one vinylic methylene at δ 128.1, two aromatic methine carbons at δ 115.5 and 113.3, two methylenes at 131.3 and 66.0, two methoxy groups at 56.2 and 56.1 ppm concluded the confirmation of structure of ester 26g.

With the above optimized reaction conditions for oxy-Michael addition (entry 3, Table II.1), the subsequent Heck coupling step was attempted. Thus, one-pot oxy-Michael addition at 50 °C for 48 h and subsequent treatment with the palladium catalyst at 80 °C for 24 h, furnished the product 23g, in moderate yield 53% (entry 4, Table II.1). Optimization was also explored for this one-pot process with other solvents and bases at varying temperatures. However, the reaction with different solvents such as THF, CH3CN and DMF failed, and by-product 24g was found to be dominant (entries 6 to 10, Table II.1). It was quite surprising to see the formation of 24g from the intermediate oxy-Michael addition product 25g. This can be explained via C-H activation, which led to a 7-membered palladacycle, which upon β-carbon cleavage would generate the cyclic palladium intermediate and resulted in aldehyde 24g. Alternately, it might also trigger a backward reaction to yield the starting material 24g via retro-oxy-Michael addition under the basic (Cs2CO3) and at hot temperature (80 °C), which, in the presence of the palladium catalyst unambiguously led to the formation of 24g.[72] The formation of 24g was further confirmed by the reaction of bromoester 25g with the palladium catalyst under similar reaction conditions. This interesting reaction in backward direction was successful, particularly with polar solvents such as DMF and CH3CN (Scheme II.11).
The formation of 24g can be justified via base triggering *retro*-oxy-Michael addition on bromoester 25g to set up an equilibration with the starting ortho-bromobenzyl alcohol 21g (Scheme II.12). Alcohol 21g reacts with the palladium catalyst and leads to the veratraldehyde 24g.

In an alternative route, the presence of a base, seven-membered palladacycle B, which may have ultimately collapsed, could give the simple benzaldehyde 24g via the palladacycle C (Scheme II.12). \(^{[72]}\)
Of these two plausible mechanisms, the one with the formation of benzyl alcohol 21g as an intermediate followed by palladium catalyzed transformation to 24g would be justified based on the reaction of a strong base with the diester 23g in dry THF at low temperature $-78 \, ^\circ\text{C}$, on treatment with NaHMDS in toluene followed by stirring at $-10 \, ^\circ\text{C}$ for 2 h, yielding the alcohol enoate 33g (Scheme II.13).

**Scheme II.13**

The formation and structural pattern of the alcoholic ester 33g was evident from the spectral data of 33g. The presence of a broad absorption band at 3485 cm$^{-1}$ due to O–H group and one strong absorption band at 1703 cm$^{-1}$ for the ester carbonyl stretching in the IR spectrum indicated the formation of the alcoholic ester 33g. In the $^1\text{H}$-NMR spectrum (Figure II.5.1), presence of two doublets at $\delta$ 7.95 and 6.29 (for two aromatic protons), five singlets at $\delta$ 7.07, 6.95 (due to two aromatic protons), $\delta$ 4.78 (for two protons of benzylic methylene group), $\delta$ 3.90 and 3.89 (due to six protons of two methoxy groups), a quartet at $\delta$ 4.24 (due to two protons of O-methylene group), one broad singlet at $\delta$ 1.89 (because of hydroxyl group) and a triplet at 1.32 ppm (for three protons of a methyl group) explained the structure of the alcoholic ester 33g. Additionally, the 13 lines of $^{13}\text{C}$-NMR spectrum (Figure II.5.2) showed the presence of five quaternary carbon resonances at $\delta$ 167.2 (due to ester carbonyl) and $\delta$ 150.8, 148.6, 133.5 and 125.1 (due to four aromatic carbons), two olefinic methines at $\delta$ 140.8 and 108.9, two aromatic methine carbons at $\delta$ 117.6 and 115.5, two aliphatic methylenes at $\delta$ 62.3 and 60.5 and of the three methyl groups, two at 55.9 (due to two methoxy groups) and one at 14.2 ppm, which confirmed the structure of ester 33g.
Figure II.5.1: $^1$H NMR (400 MHz) of compound 33g in CDCl$_3$

Figure II.5.2: $^{13}$C NMR (100 MHz) of compound 33g in CDCl$_3$

Even though, of all the screening conditions listed in Table II.1, product 23g was obtained in moderate yield (entry 4, Table II.1), it turned out to be the best optimized condition. Hence, these reaction conditions were employed for other
benzylic alcohols 21 and the results summarized in Table II.2. As anticipated, the products 23a–23h were generated in comparable to moderate yields. However, the reaction with secondary alcohol 21o furnished product 23i in inferior yield (33%). This might be due to the greater nucleophilicity of the secondary hydroxyl group that may prefer the formation of an undesired condensed by-product 26i (Table II.2).

**Table II.2:** Scope of the sequential one-pot reaction on various benzylic alcohols 21 with ethylacrylate.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>23a</td>
<td>51%</td>
</tr>
<tr>
<td>23b</td>
<td>41%</td>
</tr>
<tr>
<td>23c</td>
<td>49%</td>
</tr>
<tr>
<td>23d</td>
<td>45%</td>
</tr>
<tr>
<td>23e</td>
<td>47%</td>
</tr>
<tr>
<td>23f</td>
<td>46%</td>
</tr>
<tr>
<td>23g</td>
<td>53%</td>
</tr>
<tr>
<td>23h</td>
<td>51%</td>
</tr>
<tr>
<td>23i</td>
<td>33%</td>
</tr>
</tbody>
</table>

* Isolated yields of pure products.

After obtaining the ethyl cinnamate derivatives 23a–23i, to check the scope and generality of the method, we also attempted this sequential one-pot reaction with other Michael acceptors such as methyl acrylate and acrylonitrile. Similar results were observed even with methyl acrylate, and the products 23w and 23x were obtained in inferior yields (Table II.3). This can be ascribed to the sterically less hindered nature of methoxy group of the acrylate that may further facilitate the increased formation of the undesired by-product 26. Also, the same sort of reactivity
was noticed in case of acrylonitrile as Michael acceptor by the further dropping of yield (25%) of the corresponding product 23y (Table II.3). This low yield is could be due to the interference of the cyano group with the hydroxyl functionality.

Table II.3: Scope of the sequential one-pot reaction on various benzyl alcohols 21 with methylacrylate and acrylonitrile.

<table>
<thead>
<tr>
<th>Product</th>
<th>Isolated yield of pure products.</th>
</tr>
</thead>
<tbody>
<tr>
<td>23w (28%)</td>
<td></td>
</tr>
<tr>
<td>23x (32%)</td>
<td></td>
</tr>
<tr>
<td>23y (32%)</td>
<td></td>
</tr>
</tbody>
</table>

a Isolated yields of pure products.

After obtaining cinnamate derivatives 23a–23i, 23w, 23x and 23y, in moderate yields, we envisioned that by inhibiting the cross-condensation of the Michael acceptor with the hydroxyl group of 21, it would be possible to restrict the formation of undesired by-product 26 (Table II.1). The formation of this by-product 26 could be due to the less sterically hindered ethoxy (or methoxy) group of Michael acceptor that allowed the formation of cross-condensed undesired ester 26. Hence, it was assumed that the use of a bulky alkoxy acrylate such as tert-butyl acrylate, might preclude the formation of by-product 26, and consequently the yield of product 23 would improve. Therefore, ortho-bromobenzyl alcohols 21a–21o possessing electron-deficient as well electron-rich aromatic substituents, were treated with tert-butyl acrylate as Michael acceptor, using optimized conditions. Gratifyingly, as expected, a dramatic improvement in yield was observed and the products 23j–23v were isolated, in good to excellent yields (Table II.4).

After achieving the cinnamate derivatives 23a–23y, to further check the scope and applicability of the present method, we envisioned a divergent application
Table II.4: Scope of the sequential one-pot reaction on various benzyl alcohols 21 with tert-butyl acrylate.

![Chemical structures and yields](image)

<table>
<thead>
<tr>
<th>23a (78%)</th>
<th>23b (90%)</th>
<th>23c (87%)</th>
<th>23d (77%)</th>
<th>23e (74%)</th>
<th>23f (85%)</th>
</tr>
</thead>
</table>

$^a$ Isolated yields of pure products.

of this one-pot process for O-allylation and subsequent intramolecular Heck coupling to afford 4-methylene-3,4-dihydro-1H-isochromenes 28 directly from 2-bromobenzyl alcohols 21 (Scheme II.14). Palladium-catalyzed intramolecular Heck reaction is an efficient tool to achieve heterocyclic structures. This method has also been successfully employed for the synthesis of many natural products. Usually, these kind of systems were achieved only by a step-wise o-allylation and intramolecular Heck cyclization strategy.
Thus, synthetic trials were initiated on 2-bromobenzyl alcohol 21g using the above optimized conditions (entry 4, Table II.1). However, there was not much progress and most of the starting material of 21g was recovered (entries 1 to 4, Table II.5). Hence, we thought that the use of a stronger base would be suitable to promote the O-allylation. Therefore, alcohol 21 was treated with allyl bromide in the presence of a base NaH, in DMF. The formation of a less polar spot on TLC was indicative of the formation of O-allylation product 27g and hence, it was subjected to in-situ Heck cyclization by loading the palladium catalyst at 80 °C. It is worth mentioning after 12 h, the reaction led to the isolation of a mixture of three compounds as a regioisomeric mixture of required cyclic ethers (28 and 28') and the intermediate O-allyl ether 27g. However, increasing the reaction time of the Heck cyclization step to 24 h, furnished a regioisomeric mixture of cyclic ethers 28 and 28' in 85% yield. Of the two cyclic ethers, exo-cyclic ether 28d was formed as a major product, whereas the endo-isomer 28d' was the minor one with respect to the double bond (entry 6, Table II.5). Interestingly, both the isomers were separated by column chromatography and fully characterized. It is noteworthy that the use of quaternary ammonium salts was found to be crucial for Heck cyclization [in the present case, we used triethylbenzylammonium chloride (TEBAC)].\[\textsuperscript{23e}\] Since, it was established that the prolonged reaction time in the presence of palladium catalyst would favour the isomerization of the exo-olefin to the thermodynamically more stable endo-olefin, we decided to decrease the reaction time of Heck cyclization to control the formation of exo-olefin. However, the conversion of intermediate 27g to the final products (28 and 28') was incomplete, even after 12 h (entry 5, Table II.5).
Table II.5: Optimization of reaction conditions for sequential one-pot allylation and Heck reaction.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>3</td>
<td>Cs₂CO₃</td>
<td>toluene</td>
<td>50</td>
<td>24</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2a</td>
<td>3</td>
<td>Cs₂CO₃</td>
<td>DMF</td>
<td>80</td>
<td>48</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3a</td>
<td>3</td>
<td>Cs₂CO₃</td>
<td>DMF</td>
<td>100</td>
<td>24</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>Cs₂CO₃</td>
<td>Neat</td>
<td>80</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>NaH</td>
<td>DMF</td>
<td>RT</td>
<td>1</td>
<td>100ᵇ</td>
<td>80</td>
<td>12</td>
<td>-ᶜ</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>NaH</td>
<td>DMF</td>
<td>RT</td>
<td>1</td>
<td>100ᵇ</td>
<td>80</td>
<td>24</td>
<td>61ᵈ</td>
</tr>
</tbody>
</table>

ᵇ Isolated yields of chromatographically pure product (27g). ᵇ 100% conversion based TLC and subjected to subsequent Heck cyclization. ᵇ Products (28d and 28d') formation was observed along with the recovery of intermediate (27g). ᵇ Isolated yields of chromatographically pure products (28d and 28d').

The structure and formation of isochromene 28d was illustrated from its spectral data. The absence of a broad absorption band due to O–H group and presence of an absorption band at 1604 cm⁻¹ for the stretching of olefin in the IR spectrum predicted the formation of isochromene 28d. In the ¹H-NMR spectrum (Figure II.6.1), the absence of O–H proton resonance, the existence of eight singlets at δ 7.12, 6.48 (due to two aromatic protons), 5.42, 4.90 (because of two protons of olefinic methylene group), 4.73 (of benzylic methylene protons), 4.40 (for two
allylic methylene protons), 3.86 and 3.84 ppm (due to six protons of two O-methyl groups) elucidated the structure of isochromene 28d. Additionally, in 12 lines $^{13}$C-NMR spectrum (Figure II.6.2), the presence of five quaternary carbon resonances at $\delta$ 149.6, 148.2, 138.1, 127.6 and 123.5 (due to four aromatic carbons and one olefinic carbon), two aromatic methine carbons at $\delta$ 106.9 and 106.0, three methylenes at 104.6 (for olefin methylene), 70.8 (benzylic methylene group) and 68.7 (due to allylic methylene), two methyls at 56.0 and 55.9 ppm concluded the structure of isochromene 28d.

Similarly, the structure of the ester 28d$'$ was obvious from the spectral data. The absence of O–H group broad absorption band and the existence of olefinic absorption band at 1637 cm$^{-1}$ in the IR spectrum indicated the formation of isochromene 28d$'$. In the $^1$H-NMR spectrum (Figure II.7.1), the absence of O–H proton resonance, the presence of five singlets at $\delta$ 6.58, 6.51 (due to two aromatic protons), 4.85 (because of two protons of benzylic methylene group), 3.82 and 3.79 (due to six protons of two methoxy groups), one olefinic methine quartet at $\delta$ 6.33 and one doublet at $\delta$ 1.83 ppm due to three protons of the methyl group, established the structure of isochromene 28d$'$. Furthermore, in 11 lines $^{13}$C-NMR spectrum (Figure II.7.2), the presence of five quaternary carbon resonances at $\delta$ 148.8, 147.8, 121.0, 111.1 (due to four aromatic carbons) and 125.6 (for olefinic methine), respectively, one vinylic methine at $\delta$ 140.7, two aromatic methines at $\delta$ 108.0 and 104.9 one methylenes at 67.9, two methoxy groups at 56.1 and one methyl at 13.2 ppm confirmed the structure of isochromene 28d$'$. 
Figure II.6.1: $^1$H NMR (400 MHz) of compound 28d in CDCl$_3$

Figure II.6.2: $^{13}$CNMR (100 MHz) of compound 28d in CDCl$_3$
In order to check the generality and feasibility of the method, optimized reaction conditions were employed on various systems possessing the simple to electron-rich functionalities on the aromatic rings. The results were quite
satisfactory and furnished the corresponding isomeric products (28a–28g and 28a’–28g’) in very good yield (Table II.6).

Table II.6: Scope of the sequential one-pot O-allylation and Heck reaction on various benzyl alcohols 21.

<table>
<thead>
<tr>
<th>R²</th>
<th>R¹</th>
<th>R⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Br</td>
<td>CH₂</td>
</tr>
<tr>
<td>BnO</td>
<td>28a (62%)</td>
<td>28a’ (28%)</td>
</tr>
<tr>
<td>O</td>
<td>Br</td>
<td>CH₂</td>
</tr>
<tr>
<td>MeO</td>
<td>28b (61%)</td>
<td>28b’ (26%)</td>
</tr>
<tr>
<td>O</td>
<td>CH₂</td>
<td></td>
</tr>
<tr>
<td>28c (74%)</td>
<td>28c’ (12%)</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>MeO</td>
<td>28d (61%)</td>
<td>28d’ (24%)</td>
</tr>
<tr>
<td>MeO</td>
<td>28e (70%)</td>
<td>28e’ (13%)</td>
</tr>
<tr>
<td>O</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>MeO</td>
<td>28f (51%)</td>
<td>28f’ (22%)</td>
</tr>
<tr>
<td>O</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>MeO</td>
<td>28g (45%)</td>
<td>28g’ (32%)</td>
</tr>
</tbody>
</table>

*a* Isolated yields of pure products.

II.2.2 Synthesis of 2-Benzoxepinones:

After successfully obtaining diesters 23 and isochromens 28 and 28’, we turned our attention to extend this strategy for the concise synthesis of cyclic systems. Particularly, the retro-Michael addition of ester 23g to alcohol 33g (Scheme II.12) inspired us to investigate different base promoted cyclizations,
through the retro-Michael addition followed by a possible intramolecular oxy-Michael addition of diesters 23, for the formation of isobenzofuran systems.[76] Since the alcohol enoate 33g was the exclusive product of retro-Michael addition of 23g, in the presence of strong base NaHMDS at the low temperature range (entry 1, Table II.7; Scheme II.13), the diester 23g was subjected to the formation of initially aimed isobenzofuran 22g through an intramolecular oxy-Michael addition, in the presence of the same strong base (NaHMDS) but at 50 °C. However, the reaction under these conditions was found to be unclear and did not lead to the isolation of either the starting material 23g or any significant product (entry 2, Table II.7). Then the diester 23g was subjected to the same type of degradation under established conditions of the diester 23g formation without the palladium catalyst, with base Cs2CO3 at 80 °C in toluene in order to ensure the stability of the diester 23g. As expected, the reaction showed no progress under these conditions and confirmed the inertness of esters (entry 3, Table II.7). We anticipated that the rise in temperature might activate the diester 23g towards degradation (retro-oxy-Michael addition) followed by intramolecular cyclization. As expected, at 120 °C after 24 h, in toluene, the reaction yielded the isobenzofuran 22g, albeit in poor yield along with an unexpected seven-membered lactenone 33g (entry 4, Table II.7). As the retro-Michel addition was favoured in polar solvents, the solvent was changed from toluene to DMF and subjected the reaction at both 80 °C and 120 °C. Interestingly, switching to polar solvent proved to be beneficial and furnished the lactenone product 34g exclusively, in good yield (entries 5 and 6, Table II.7). Moreover, the reaction in DMF at 120 °C was completed within 12 h, whereas, at 80 °C, it took up to 24 h.

The structure and formation of the isobenzofuran 22g was apparent from the spectral data of 22g. The presence of strong absorption band at 1728 cm−1 for the ester carbonyl in the IR spectrum predicted the formation of the isobenzofuran 22g. In the 1H-NMR spectrum (Figure II.8.1), the absence of O–H proton resonance, the presence of four singlets at δ 6.72, 6.70 (due to two aromatic protons), 3.86 and 3.84 ppm (due to six protons of two methoxy groups), a multiplet in the region δ 5.65–
5.55 due to methine of furan ring, three doublet of doublets at 5.08, 5.00 (due to two benzylic methylene protons) and 2.72 (due to two protons of methylene moiety), one quartet at δ 4.18 (for two protons of O-methylene) and a triplet at 1.25 ppm for the methyl clarified the structure of the isobenzofuran 22g. Moreover, in 14 lines of \(^{13}\)C-NMR spectrum (Figure II.8.2), five quaternary carbon resonances at δ 170.9 (due to ester carbonyl), 149.3, 148.9, 132.2 and 130.6 (due to four aromatic carbons), three methine carbons at δ 104.2, 103.9 (for two aromatic carbons) and 80.6 (of aliphatic methane), three methylenes at 72.8 (benzylic methylene group), 60.6 and 41.8 (for two aliphatic methylenes), a methyl at 14.2 ppm confirmed the structure of isobenzofuran 22g.

**Table II.7:** Screening reaction conditions for the synthesis of 34g starting from 23g.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base [2 equiv]</th>
<th>Solvent [2 mL]</th>
<th>Temp [°C]</th>
<th>Time [h]</th>
<th>Yield 33g [%](^a)</th>
<th>Yield 22g [%](^a)</th>
<th>Yield 34g [%](^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHMDS</td>
<td>toluene</td>
<td>−78 to −10</td>
<td>12</td>
<td>69</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS</td>
<td>toluene</td>
<td>50</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cs(_2)CO(_3)</td>
<td>toluene</td>
<td>80</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cs(_2)CO(_3)</td>
<td>toluene</td>
<td>120</td>
<td>24</td>
<td>16</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Cs(_2)CO(_3)</td>
<td>DMF</td>
<td>120</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>Cs(_2)CO(_3)</td>
<td>DMF</td>
<td>80</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^a\)Yields of chromatographically isolated pure products.

In the same way the structure of lactenone 34g was obvious from the spectral data of 34g. The existence of a strong absorption band at 1693 cm\(^{-1}\) for the
Figure II.8.1: $^1$H NMR (400 MHz) spectrum of 22g in CDCl$_3$

Figure II.8.2: $^{13}$C NMR (100 MHz) spectrum of 22g in CDCl$_3$
carbonyl of ester and olefinic absorption band at 1603 cm$^{-1}$ in the IR spectrum indicated the formation of the lactenone 34g. In the $^1$H-NMR spectrum (Figure II.9.1), the presence of two doublets at $\delta$ 7.12 and 6.26 due to olefinic protons, five singlets at $\delta$ 6.90, 6.87 (due to two aromatic protons), 4.98 (because of two protons
of benzylic methylene group), 3.93 and 3.90 ppm (due to six protons methoxy groups) established the structure lactenone \textbf{34g}. Furthermore, in 12 lines $^{13}$C-NMR spectrum (Figure II.9.2), presence of five quaternary carbon resonances at $\delta$ 168.0 (due to the ester cabonyl), 150.3, 149.7, 128.7 and 128.6 (due to four aromatic carbons), four methines at $\delta$ 140.6, 120.9 (for two olefinic methines), 112.1 and 111.3 (because of two aromatic methines), respectively. One methylene at 68.3, two methoxy groups at 56.2 and 56.1 ppm proved the structure of lactenone \textbf{34g}.

Quite interestingly, it was found in the literature that this lactenone \textbf{34} skeleton formed the core of a few natural products and biologically active compounds with this lactenone \textbf{34} skeleton. For example, these lactenones or 2-benzoxepin-3(1\textit{H})-ones \textbf{34} exist as the core structure in antibiotics xylarinol (A) \textbf{29} and xylarinol (B) \textbf{30},\textsuperscript{[77]} and as part of the structure in new tyrosine kinase (p56lck) inhibitor ulocladol \textbf{31}\textsuperscript{[78]} and cytotoxic alterlactone \textbf{32}\textsuperscript{[79]} (Figure II.10). Moreover, analogues of these 2-benzoxepin-3(1\textit{H})-ones \textbf{34} have been recognized to display good analgesic activities.\textsuperscript{[80]}

![Diagram](Figure II.10)

The interesting structure of lactenone \textbf{34g} present in naturally occurring compounds and the promising biological activities of their analogues made us synthesize more functionalized 2-benzoxepinones. After successfully obtaining lactenone \textbf{34g} by performing the reaction on an isolated diester \textbf{23g}, in order to make the method more efficient, we decided to perform the reaction in a domino
sequential one-pot manner by starting directly from ortho-bromobenzyl alcohols 21 (Scheme II.15).

![Scheme II.15](image)

It is very evident that the established method yields the diesters 23 via sequential one-pot intermolecular oxy-Michael addition followed by an intermolecular Heck reaction of 2-bromobenzyl alcohols 21. The present study was sketched to extend the so formed diesters 23 to lactenones 34 by in-situ intramolecular degradation (retro-oxy-Michael addition) and subsequent condensation promoted by base. However, there is a challenge that limits the use of a single solvent system to conduct all these reaction steps in a sequential one-pot method. For example, toluene was identified as the solvent suitable for oxy-Michael addition and succeeding Heck coupling, but not an appropriate solvent for the final retro-Michael addition and condensation; on the other hand, DMF was found to be an ideal solvent for the final cyclization to yield lactenone 34g but not suitable for the formation of the diester 23g. Hence, the choice of solvent was crucial and it was decided to implement toluene as the first solvent until the formation of the diester 23g and then DMF as the second solvent system in order to promote the final cyclization from the diester 23g to yield the lactenone 34g. Since the formation of lactenone 34g formation was at 120 °C in toluene (entry 4, Table II.7), the final cyclization was conducted at the same temperature after addition of DMF to the reaction mixture soon after the formation of diesters 23 (Scheme II.16).
Based on the above knowledge, we proceeded as planned for the sequential one-pot synthesis of functionalized lactenones 34 by starting reaction between different benzyl alcohols 21 and ethyl acrylate. Agreeably, the reaction was quite successful and furnished cyclic lactenones 34a–34h in moderate yields (Table II.8). Though moderate, the yields were still in an acceptable range, because it was the overall yield of the sequence after three individual reaction steps (i.e. every individual step approximately accounts for 75%), since this kind of systems were achieved in not less than three individual reactions.

**Table II.8:** Scope of the sequential one-pot Michael addition, Heck reaction, degradation and condensation from various benzyl alcohols 21.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34a</td>
<td>46%</td>
</tr>
<tr>
<td>34b</td>
<td>40%</td>
</tr>
<tr>
<td>34c</td>
<td>46%</td>
</tr>
<tr>
<td>34d</td>
<td>42%</td>
</tr>
<tr>
<td>34e</td>
<td>44%</td>
</tr>
<tr>
<td>34f</td>
<td>44%</td>
</tr>
<tr>
<td>34g</td>
<td>48%</td>
</tr>
<tr>
<td>34h</td>
<td>47%</td>
</tr>
</tbody>
</table>

*Yields of chromatographically isolated pure products.*
After achieving 2-benzoxepinones 34a–34h from ethyl diesters 23a–23h we turned our interest towards the synthesis of lactenones 34 from tert-butyl diesters 23 and the esters of secondary alcohols 23. Since it is well established that the sequential one-pot synthesis of diesters 23 is quite successful and yields excellent results with the bulkier tert-butyl acrylate as the Michael acceptor, we also expected the subsequent intramolecular cyclization in a sequential one-pot synthesis would be amenable to give the lactenones 34 in the manner similar to that used in case of ethyl acrylate. Hence, the 2-bromobenzyl alcohol 21g was subjected for direct sequential one-pot formation of lactenone 34g, under optimized conditions by using tert-butyl acrylate as Michael acceptor. However, the sequential one-pot reaction between

![Diagram](image)

Scheme II.17

2-bromobenzyl alcohol 21g and tert-butyl acrylate, under standard reaction conditions, was impeded after the formation of the diester 23s (Scheme II.17).

On the other hand, the reaction with isolated diester 23s, in the polar solvent, DMF, was also unable to produce the lactenone 34g as an exclusive product; rather unexpectedly furnishing three products (entry 3, Table II.9). This might be due to the release of strong base CsO'Bu at the end of the lactenone 34g formation, and might have reverted the 2-benzoxepinone 34g to the acyclic alcohol enoate 33s and the isobenzofuran 22s. In another way, the bulky tertiary butyl group might have impeded final cyclization, after the initial cyclization (isobenzofuran ring formation) and induced ring opening through double bond isomerization. The reaction, when performed at higher temperature, also failed to produce any corresponding product (entry 7 and 8, Table II.9). The use of a much stronger base such as NaHMDS did
Table II.9: Screening of reaction conditions, for the synthesis of 2-benzocepoxinone 34g from the tertiary butyl diester 23s.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Solvent (mL)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Recovery of 23s (%)</th>
<th>Yield 33s (%)a</th>
<th>Yield 22s (%)a</th>
<th>Yield 34g (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs₂CO₃ (2)</td>
<td>toluene (2)</td>
<td>80</td>
<td>48</td>
<td>93</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃ (2)</td>
<td>toluene (2)</td>
<td>100</td>
<td>48</td>
<td>83</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cs₂CO₃ (3)</td>
<td>DMF (2)</td>
<td>80</td>
<td>24</td>
<td>-</td>
<td>9b</td>
<td>28</td>
<td>18b</td>
</tr>
<tr>
<td>4</td>
<td>Cs₂CO₃ (3)</td>
<td>CH₃CN (2)</td>
<td>80</td>
<td>24</td>
<td>-</td>
<td>0</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>Cs₂CO₃ (3)</td>
<td>DMF (2)</td>
<td>140</td>
<td>3</td>
<td>-</td>
<td>15b</td>
<td>23</td>
<td>40b</td>
</tr>
<tr>
<td>6</td>
<td>Cs₂CO₃ (1.5)</td>
<td>xylene (2)</td>
<td>130</td>
<td>48</td>
<td>30</td>
<td>0</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>7c</td>
<td>Cs₂CO₃ (3)</td>
<td>DMA (2)</td>
<td>160</td>
<td>12</td>
<td>-d</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Cs₂CO₃ (3)</td>
<td>DMSO (2)</td>
<td>160</td>
<td>12</td>
<td>-d</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>NaHMDS (4)</td>
<td>toluene (2)</td>
<td>50</td>
<td>12</td>
<td>-d</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Cs₂CO₃ (3)</td>
<td>DMF (2)</td>
<td>120</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>73</td>
</tr>
</tbody>
</table>

a Yields of chromatographically isolated pure products. b Yields of the products based on ¹H NMR. c Yields based on the recovery of the starting material (30%). d Reaction was not clean.
not yield anything fruitful (entry 9, Table II.9). However, the reaction under the usual conditions for a prolonged time in DMF facilitated the 2-benzoepinepinone 34g as an exclusive product in good yield (entry 10, Table II.9).

A similar problem was encountered with the diethyl/di-tert-butyl esters of secondary alcohols 23v, 23z, 23aa and 2ab. Hence, in these cases the separate base induced cyclization was applied to these diesters 23v, 23z, 23aa and 2ab (entry 6, Table II.3). As a result, the corresponding lactenones 34 were obtained in moderate to good yields (Table II.10).

**Table II.10: Step-wise formation of lactenones 34 from the diesters 23.**

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;, R&lt;sup&gt;2&lt;/sup&gt;, R&lt;sup&gt;3&lt;/sup&gt;, R&lt;sup&gt;4&lt;/sup&gt;, EWG</th>
<th>34g (73%)</th>
<th>34i (55%)</th>
<th>34j (52%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO, MeO, O, O</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>Me, Me, O, O</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>MeO, Me, O, O</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td></td>
</tr>
</tbody>
</table>

*Yields of chromatographically isolated pure products.*

After successfully obtainig lactenones 34 starting from primary and secondary alcohols 21, we were interested in studying the mechanistic aspects of the formation of lactenones 34. In order to understand the reaction mechanism for their formation, we separately subjected the isolated alcohol esters 23g and 23s to condensation. According to our expectation, the process afforded the lactenone 34g in good yield in both cases (Scheme II.18).
To further confirm the mechanism of the reaction, chromatographically isolated pure cyclic ether $22_g$, which was prepared by the conditions of entry 4 in Table II.7, was also subjected to lactenone $34_g$ formation. In support of our hypothesis, the reaction furnished the expected lactenone $34_g$ (Scheme II.19).

In addition, the products obtained by the degradation of diester $23_s$ on treatment with Cs$_2$CO$_3$ in DMF at 80 °C for 24 h (entry 3, Table II.9), i.e., isolated cyclic ether $22_s$ and the inseparable mixture of alcohol $33_s$ and lactenone $34_g$ were treated separately again with Cs$_2$CO$_3$ in DMF at 120 °C for 48 h (entry 10, Table II.9), to give the lactenone $34_g$ as expected (Scheme II.20).
Based on the above experimental studies, the possible reaction mechanism for the formation of 34g from 23g is as depicted in Scheme II.20. After the formation of oxy-Michael product 25g, and subsequent Heck coupling gives 23g. At this stage, the base may trigger retro-oxy-Michael addition (E₂-elimination) of 23g and an intramolecular oxy-Michael addition of the resulted alkoxide would lead to cyclic enolate H. Now, the cycloreversion of the enolate H intermediate can set up an equilibration with its acyclic alkoxide I through possible E- to Z-isomerization of the cinnamate double bond. Finally, intramolecular condensation of the intermediate product I produces the lactenone 34g.
In addition to NMR and other spectroscopic studies for structural elucidation, the structure of lactenone 34 was further unambiguously confirmed by single-crystal X-ray diffraction analysis of 34c (Figure II.11).

**Scheme II.21**

Figure II.11: X-ray crystal structure of 34c. Thermal ellipsoids are drawn at 50% probability level.

**II.3. CONCLUSIONS:**

To conclude, an efficient domino sequential one-pot C–O and C–C bond formation via an intermolecular base mediated oxy-Michael addition/O-allylation
and subsequent inter/intra-molecular Heck reaction for the synthesis of functionalized cinnamates from simple 2-bromobenzyl alcohols was developed. Notably, for the preparation of cinnamate diesters, sterically hindered tert-butyl acrylate was identified as the ideal Michael acceptor. On the other hand, the reaction with less sterically hindered ethyl/methyl acrylates or acrylonitrile gave the product in moderate yield, which can be justified due to their less steric nature, allowing them to participate in the condensation as a competing reaction. This method was also applied to the efficient synthesis of isochromenes via sequential O-allylation and intramolecular Heck coupling. Furthermore, this method was successfully applied to the synthesis of functionalized 2-benzoquinone-3(1H)-ones in a novel domino reaction sequence, via an intermolecular oxy-Michael addition, intermolecular Heck coupling and intramolecular degradation (retro-oxy-Michael addition) followed by condensation. Quite interestingly, the 2-benzoquinone-3(1H)-ones are present as the major structural core of naturally occurring as well as analogous compounds, exhibiting interesting biological properties. Notably, a remarkable solvent effect was observed in order to promote the final intramolecular degradation followed by condensation, for the synthesis of 2-benzoquinone-3(1H)-ones. The initial two steps involved a straightforward construction of C–O and C–C bonds for formation of the diesters, whereas the final cyclization involved a novel mechanistic path, a base promoted intramolecular degradation, double bond isomerization and condensation.

**Synthesis of cinnamates and isochromenes**

![Sequential one-pot](image-url)
**Synthesis of 2-benzoxepinones**

![Sequential one-pot reaction diagram]

**II.4 EXPERIMENTAL SECTION:**

**General:**
IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. $^1$H-NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in CDCl$_3$; chemical shifts ($\delta$ in ppm) and coupling constants ($J$ in Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) ($\delta_H = 0.00$ ppm) or CHCl$_3$ ($\delta_H = 7.25$ ppm). $^{13}$C-NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at room temperature in CDCl$_3$; chemical shifts ($\delta$ in ppm) are reported relative to CHCl$_3$ [ $\delta_C = 77.00$ ppm (central line of triplet)]. In the $^{13}$C-NMR, the nature of carbons (C, CH, CH$_2$, and CH$_3$) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH$_2$) and q = quartet (for CH$_3$). In the $^1$H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by $^1$H, $^{13}$C CPD (Carbon Proton Decoupling) and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF using multimode source. All small scale dry reactions were carried out using Schlenk tube technique. Reactions were monitored by TLC on silica gel using a mixture of petroleum ether and ethyl acetate as eluents. Reactions were generally run under an argon or nitrogen
atmosphere. Solvents such as petroleum ether, ethyl acetate and dichloromethane were distilled prior use. Petroleum ether with a boiling range of 60 to 80 °C was used. Diethyl ether and toluene were dried over benzophenone/sodium. DMF was dried over calcium hydride. 2-Bromobenzaldehyde and other aromatic aldehydes were purchased from local commercial sources and used as received. Acme’s silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

II.4.1 SYNTHESIS OF DIESTERS AND ISOCHROMENES:

General Procedure for the Preparation of Alcohols (GP-1):

To an ice cold, magnetically stirred solution of a 2-bromobenzaldehyde 35 (500 mg, 1.56–2.70 mmol) in methanol (15–20 mL), was added sodium borohydride (2.73–4.05 mmol). Then the reaction mixture was allowed to attain room temperature and stirred for 1 h. Solvent was removed under reduced pressure, treated with aqueous NH₄Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol 21 (77–98%).

General Procedure for Intermolecular Oxy-Michael Addition followed by an Intermolecular Heck reaction (GP-2):

In an oven dried round bottomed flask fitted with a rubber septum, were added alcohol 21 (100 mg, 0.31–0.53 mmol), alkyl acrylate (methyl, ethyl and tertiary butyl acrylate, or acrylo–nitrile) (1.55–2.67 mmol) and Cs₂CO₃ (0.62–1.07 mmol) followed by addition of toluene (2 mL) at room temperature under a nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (10 mol%) and PPh₃ (20 mol%) under nitrogen atmosphere. The stirred
reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. Then, the mixture was cooled to room temperature, treated with aqueous NH₄Cl solution and then extracted with CH₂Cl₂ (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the product 23 (25–90%).

**General Procedure for Intermolecular O-allylation followed by an Intramolecular Heck reaction (GP-3):**

In an oven dried round bottomed flask fitted with a rubber septum, were added alcohol 21 (100 mg, 0.30–0.46 mmol), NaH (1.20–1.84 mmol) and DMF (3 mL) followed by addition of allylbromide (0.60–0.92 mmol) at room temperature under a nitrogen atmosphere. The suspension was allowed to stir at the same temperature for 1 h. Progress of the allylation was monitored by TLC till the reaction is completed. To the reaction mixture, cooled at room temperature, were added Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%) triethylbenzylammonium chloride (0.30–0.46 mmol) under a nitrogen atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. The mixture was cooled to room temperature, treated with aqueous NH₄Cl solution and then extracted with CH₂Cl₂ (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the isochromenes 28’ (12–32%) as a viscous liquid or a semi-solid. Further elution of crude material by silica gel column chromatography (petroleum ether/ethyl acetate) yielded isochromenes 28 (45–78%) as a viscous liquid or a semi-solid.

The following bromobenzaldehydes 35b–35h from table were synthesized using literature reported bromination of corresponding benzaldehydes.⁸¹
Primary alcohols ortho-bromobenzyl alcohols 21a–21o required as precursors for this study, were synthesized using reduction reaction on corresponding 2-bromobenzaldehydes 35a–35h with the reducing agent NaBH₄. The secondary alcohols 21k–21o, were obtained using standard methyl Grignard addition to the 2-bromobenzaldehydes (35a, 35c, 35e, 35f & 35g).

Compounds 21a[82], 21b[83], 21c[84], 21f[85], 21g[86], 21h[87], 21i[88], 21j[89] and 21k–21o[90] are known in the literature.
[5-(Benzyloxy)-2-bromo-4-methoxyphenyl]methanol (21d):

GP-1 was carried out with the 2-bromobenzaldehyde 35d (500 mg, 1.56 mmol), NaBH₄ (117 mg, 3.12 mmol) in methanol (15 mL). The resulted ice cold mixture was allowed to attain room temperature and stirred for 1 h. Purification of the crude material by silica gel column (petroleum ether/ethyl acetate, 90:10 to 70:30) furnished the alcohol 21d (440 mg, 87%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 112–115 °C). [TLC control (petroleum ether/ethyl acetate 70:30), Rf(35d)=0.65, Rf(21d)=0.40, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): v_max=3372, 2926, 1601, 1501, 1456, 1439, 1381, 1259, 1209, 1156, 1054, 1028, 855, 798, 738, 697 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.42 (d, 2H, J=7.3 Hz, Ar-H), 7.36 (d, 1H, J=7.3 Hz, Ar-H), 7.35 (d, 1H, J=7.3 Hz, Ar-H), 7.29 (t, 1H, J=7.3 Hz, Ar-H), 7.02 (s, 2H, Ar-H), 5.11 (s, 2H, Ar-CH₂OPh), 4.59 (s, 2H, Ar-CH₂OH), 3.85 (s, 3H, Ar-OCH₃), 2.05 (br. s, 1H, OH) ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=149.6 (s, Ar-C), 147.6 (s, Ar-C), 136.6 (s, Ar-C), 131.7 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 115.8 (d, Ar-CH), 114.4 (d, Ar-CH), 113.1 (s, Ar-C), 71.1 (t, Ar-CH₂OPh), 64.7 (t, Ar-CH₂OH), 56.2 (q, Ar-OCH₃) ppm.

HR-MS (ESI⁺): m/z calculated for [C₁₅H₁₄BrO₂]⁺=[(M+H)–H₂O]⁺: 305.0172; found 305.0173.

[4-(Benzyloxy)-2-bromo-5-methoxyphenyl]methanol (21e):

GP-1 was carried out with the 2-bromobenzaldehyde 35e (500 mg, 1.56 mmol), NaBH₄ (117 mg, 3.12 mmol) in methanol (15 mL). The resulted ice cold mixture was allowed to attain room temperature and stirred for 1 h. Purification of the crude material by silica gel column (petroleum ether/ethyl acetate, 90:10 to
70:30) furnished the alcohol 21e (470 mg, 93%) as a white solid, recrystallized from dichloromethane/ hexane (m. p. 102–108 °C). [TLC control (petroleum ether/ethyl acetate 70:30), \( R_f(35e)=0.65, R_f(21e)=0.40 \), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \( \nu_{max}=3392, 2934, 1600, 1501, 1459, 1385, 1260, 1159, 1050, 1011, 859, 744, 698 \text{ cm}^{-1} \).

**\(^1\)H-NMR (CDCl\(_3\), 400 MHz)**: \( \delta=7.42 \text{ (d, 2H, } J=7.0 \text{ Hz, Ar-H)}, 7.37 \text{ (d, 1H, } J=7.0 \text{ Hz, Ar-H)}, 7.36 \text{ (d, 1H, } J=7.0 \text{ Hz, Ar-H)}, 7.31 \text{ (t, 1H, } J=7.0 \text{ Hz, Ar-H)}, 7.04 \text{ (s, 1H, Ar-H)}, 7.01 \text{ (s, 1H, Ar-H)}, 5.09 \text{ (s, 2H, Ar-CH\(_2\)OPh)}, 4.64 \text{ (s, 2H, Ar-CH\(_2\)OH)}, 3.86 \text{ (s, 3H, Ar-OCH\(_3\))}, 2.14 \text{ (br. s, 1H, OH)} \text{ ppm.}

**\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz)**: \( \delta=149.2 \text{ (s, Ar-C)}, 148.0 \text{ (s, Ar-C)}, 136.3 \text{ (s, Ar-C)}, 132.4 \text{ (s, Ar-C)}, 128.6 \text{ (d, 2C, Ar-CH)}, 128.0 \text{ (d, Ar-CH)}, 127.4 \text{ (d, 2C, Ar-CH)}, 117.9 \text{ (d, Ar-CH)}, 112.3 \text{ (d, Ar-CH)}, 112.2 \text{ (s, Ar-C)}, 71.2 \text{ (t, Ar-CH\(_2\)OPh)}, 64.8 \text{ (t, Ar-CH\(_2\)OH)}, 56.1 \text{ (q, Ar-OCH\(_3\))} \text{ ppm.}

**HR-MS (ESI\(^+\))**: \( m/z \text{ calculated for } [C_{15}H_{14}BrO_2]^+=[(M+H)–H_2O]^+: 305.0172; \text{ found 305.0175.}

![2-Bromo-4,5-dimethoxybenzyl but-3-enoate (26g)](image)

**2-Bromo-4,5-dimethoxybenzyl but-3-enoate (26g):**

In an oven dried round bottomed flask fitted with a rubber septum, were added alcohol 21g (100 mg, 0.40 mmol), ethyl acrylate (203 mg, 2.02 mmol) and Cs\(_2\)CO\(_3\) (264 mg, 0.81 mmol) followed by addition of toluene (2 mL) at room temperature under a nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till it is completed. The reaction mixture was cooled to room temperature, treated with aqueous NH\(_4\)Cl and extracted with CH\(_2\)Cl\(_2\) (3 \times 10 \text{ mL}). The organic layers were washed with saturated NaCl solution, dried (Na\(_2\)SO\(_4\)) and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 89:11) furnished the condensed ester product 26g (19.5 mg, 16%) as minor product,
as semi-solid. [TLC control (petroleum ether/ethyl acetate 70:30), \( R_f(21g) = 0.40 \),
\( R_f(26g) = 0.62 \), UV detection].

**IR (neat; MIR-ATR, 4000–6000 cm\(^{-1}\))**: \( \nu_{max} = 2934, 2843, 1722, 1680, 1601, 1504, 1461, 1383, 1260, 1211, 1163, 1030, 801 \) cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.03 \) (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H),
6.45 (dd, 1H, \( J = 17.3 \) and 1.2 Hz, O=C-CH=CH\(_2\)(trans)), 6.16 [dd, 1H, \( J = 17.3 \) and
10.3 Hz, O=C-CH\(_2\)CH\(_2\)], 5.85 [dd, 1H, \( J = 10.3 \) and 1.2 Hz, O=C-CH=CH\(_2\)(cis)],
5.21 (s, 2H, Ar-CH\(_2\)OC=O), 3.86 (s, 3H, Ar-OCH\(_3\)), 3.86 (s, 3H, Ar-OCH\(_3\)) ppm.

\(^13\)C-NMR (CDCl\(_3\), 100 MHz): \( \delta = 165.9 \) (s, O=C–O), 149.6 (s, Ar-C), 148.3
(s, Ar-C), 131.3 (t, O=C-OCH=CH\(_2\)), 128.1 (d, O=C-OCH=CH\(_2\)), 127.0 (s, Ar-C),
115.5 (d, Ar-CH), 114.4 (s, Ar-C), 113.3 (d, Ar-CH), 66.0 (t, Ar-CH\(_2\)OC=O), 56.2
(q, Ar-OCH\(_3\)), 56.1 (q, Ar-OCH\(_3\)) ppm.

**Ethyl 3-[(2-bromo-4,5-dimethoxybenzyl)oxy]propanoate (25g):**

Further elution of crude material by silica gel column chromatography
(petroleum ether/ethyl acetate, 89:11 to 80:20) yielded Michael addition product 25g
(110 mg, 78%) as major product, as pale yellow viscous liquid. [TLC control
(petroleum ether/ethyl acetate 70:30), \( R_f(21g) = 0.40 \), \( R_f(25g) = 0.60 \), UV detection].

**IR (neat; MIR-ATR, 4000–6000 cm\(^{-1}\))**: \( \nu_{max} = 2933, 2848, 1732, 1602, 1505, 1463, 1440, 1381, 1260, 1185, 1161, 1107, 1030, 860, 800 \) cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \( \delta = 6.98 \) (s, 2H, Ar-H), 4.52 (s, 2H, Ar-
CH\(_2\)OCH\(_2\)), 4.14 (q, 2H, \( J = 7.2 \) Hz, OCH\(_2\)CH\(_3\)), 3.86 (s, 3H, Ar-OCH\(_3\)), 3.84 (s, 3H,
Ar-OCH\(_3\)), 3.79 (t, 2H, \( J = 6.3 \) Hz, OCH\(_2\)CH\(_2\)COOEt), 2.62 (t, 2H, \( J = 6.3 \) Hz,
OCH\(_2\)CH\(_2\)COOEt), 1.24 (t, 3H, \( J = 7.2 \) Hz, OCH\(_2\)CH\(_3\)) ppm.

\(^13\)C-NMR (CDCl\(_3\), 100 MHz): \( \delta = 171.5 \) (s, O=C–O), 148.8 (s, Ar-C), 148.5
(s, Ar-C), 129.4 (s, Ar-C), 115.2 (d, Ar-CH), 112.7 (s, Ar-C), 111.9 (d, Ar-CH), 72.0
(t, Ar-CH\(_2\)OCH\(_2\)), 65.9 (t, OCH\(_2\)CH\(_2\)COOEt), 60.5 (t, OCH\(_2\)CH\(_3\)), 56.1 (q, Ar-
OCH\(_3\)), 56.0 (q, Ar-OCH\(_3\)), 35.1 (t, OCH\(_2\)CH\(_2\)COOEt), 14.2 (q, OCH\(_2\)CH\(_3\)) ppm.

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HR-MS (ESI\(^+\)): m/z calculated for [C\(_{14}\)H\(_{19}\)BrNaO\(_5\)]\(^+\)=[M+Na\(^+\)]: 369.0308; found 369.0307.

Ethyl (2E)-3-[2-[1-(3-ethoxy-3-oxopropoxy)methyl]phenyl]acrylate (23a):

GP-2 was carried out with the 2-bromobenzyl alcohol 21a (100 mg, 0.53 mmol), ethyl acrylate (268 mg, 2.67 mmol) and Cs\(_2\)CO\(_3\) (349 mg, 1.07 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)\(_2\) (12.0 mg, 10 mol%) and PPh\(_3\) (28.1 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester 23a (84.0 mg, 51%) as a colorless viscous oil. [TLC control (petroleum ether/ethyl acetate 85:15), \(R_f\)(21a)=0.45, \(R_f\)(23a)=0.44, UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \(\nu_{max}\)=2980, 2935, 2872, 1731, 1711, 1634, 1602, 1368, 1313, 1268, 1176, 1095, 1031, 766 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta=7.96\) (d, 1H, \(J=15.9\) Hz, CH=CHCOOEt), 7.57 (dd, 1H, \(J=7.4\) and 1.6 Hz, Ar-H), 7.42–7.26 (m, 3H, Ar-H), 6.35 (d, 1H, \(J=15.9\) Hz, CH=CHCOOEt), 4.63 (s, 2H, Ar-CH\(_2\)OCH\(_2\)), 4.25 (q, 2H, \(J=7.1\) Hz, OCH\(_2\)CH\(_3\)), 4.13 (q, 2H, \(J=7.1\) Hz, OCH\(_2\)CH\(_2\)OCH\(_2\)COOEt), 3.78 (t, 2H, \(J=6.5\) Hz, OCH\(_2\)CH\(_2\)OCH\(_2\)COOEt), 2.61 (t, 2H, \(J=6.5\) Hz, OCH\(_2\)CH\(_2\)OCH\(_2\)COOEt), 1.33 (t, 3H, \(J=7.1\) Hz, OCH\(_2\)CH\(_3\)), 1.23 (t, 3H, \(J=7.1\) Hz, OCH\(_2\)CH\(_3\)) ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta=171.4\) (s, O=C–O), 166.8 (s, O=C–O), 141.5 (d, CH=CHCOOEt), 136.8 (s, Ar-C), 133.5 (s, Ar-C), 129.8 (d, CH=CHCOOEt), 129.3 (d, Ar-CH), 128.3 (d, Ar-CH), 126.7 (d, Ar-CH), 120.1 (d, Ar-CH), 70.8 (t, Ar-CH\(_2\)OCH\(_2\)), 65.9 (t, OCH\(_2\)CH\(_2\)OCH\(_2\)COOEt), 60.5 (2 \(\times\) t, 2C, OCH\(_2\)CH\(_3\)), 35.1 (t, OCH\(_2\)CH\(_2\)OCH\(_2\)COOEt), 14.3 (q, OCH\(_2\)CH\(_3\)), 14.2 (q, OCH\(_2\)CH\(_3\)) ppm.
Ethyl (2E)-3-{4-(benzyloxy)-2-[1-(3-ethoxy-3-oxopropoxy)methyl]phenyl}acrylate (23b):

GP-2 was carried out with the 2-bromobenzyl alcohol 21b (100 mg, 0.36 mmol), ethyl acrylate (179 mg, 1.79 mmol) and Cs\(_2\)CO\(_3\) (234 mg, 0.72 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)\(_2\) (8.0 mg, 10 mol%) and PPh\(_3\) (18.8 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester 23b (58 mg, 41%) as a yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), \(R_f\)(21b)=0.45, \(R_f\)(23b)=0.45, UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \(\nu_{max}=2980, 2930, 1730, 1714, 1634, \) 1602, 1311, 1257, 1176, 1096, 1029, 763 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta=7.88\) (d, 1H, \(J=15.8\) Hz, CH=CHCOOEt), 7.54 (d, 1H, \(J=8.5\) Hz, Ar-H), 7.46–7.26 (m, 5H, Ar-H), 7.05 (d, 1H, \(J=2.5\) Hz, Ar-H), 6.89 (dd, 1H, \(J=8.5\) Hz and 2.5 Hz, Ar-H), 6.26 (d, 1H, \(J=15.8\) Hz, CH=CHCOOEt), 5.09 (s, 2H, PhOCH\(_2\)Ar), 4.63 (s, 2H, Ar-CH\(_2\)OCH\(_2\)H), 4.25 (q, 2H, \(J=7.2\) Hz, OCH\(_2\)CH\(_3\)), 4.14 (q, 2H, \(J=7.2\) Hz, OCH\(_2\)CH\(_3\)), 3.78 (t, 2H, \(J=6.5\) Hz, OCH\(_2\)CH\(_2\)COOEt), 2.61 (t, 2H, \(J=6.5\) Hz, OCH\(_2\)CH\(_2\)COOEt), 1.33 (t, 3H, \(J=7.2\) Hz, OCH\(_2\)CH\(_3\)), 1.24 (t, 3H, \(J=7.2\) Hz, OCH\(_2\)CH\(_3\)) ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta=171.4\) (s, O=C–O), 167.1 (s, O=C–O), 160.2 (s, Ar-C), 140.8 (d, CH=CHCOOEt), 139.0 (s, Ar-C), 136.5 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.3 (d, Ar-CH), 128.0 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 125.8 (s, Ar-C), 117.7 (d, CH=CHCOOEt), 114.9 (d, Ar-CH), 114.5 (d, Ar-CH), 70.5 (t, PhCH\(_2\)OAr), 70.0 (t, Ar-CH\(_2\)OCH\(_2\)), 66.0 (t, OCH\(_2\)CH\(_2\)COOEt), 60.5 (t, OCH\(_2\)CH\(_3\)).
60.3 (t, OCH$_2$CH$_3$), 35.0 (t, OCH$_2$CH$_2$COOEt), 14.3 (q, OCH$_2$CH$_3$), 14.1 (q, OCH$_2$CH$_3$) ppm.

**HR-MS (ESI$^+$):** m/z calculated for [C$_{24}$H$_{28}$NaO$_6$]$^+$=[M+Na]$^+$: 435.1778; found 435.1781.

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**Ethyl (2E)-3-[2-[1-(3-ethoxy-3-oxopropoxy)methyl]-4-methoxyphenyl]acrylate (23c):**

GP-2 was carried out with the 2-bromobenzyl 21c (100 mg, 0.46 mmol), ethyl acrylate (231 mg, 2.30 mmol) and Cs$_2$CO$_3$ (300 mg, 0.92 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)$_2$ (10.3 mg, 10 mol%) and PPh$_3$ (24.2 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester 23c (76.2 mg, 49%) as a colorless viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), $R_f$(21c)=0.43, $R_f$(23c)=0.43, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{max}$=2980, 2930, 1732, 1710, 1632, 1604, 1599, 1179, 1161, 1096, 1034, 861 cm$^{-1}$.

**$^1$H-NMR (CDCl$_3$, 400 MHz):** $\delta$=7.86 (d, 1H, $J$=15.8 Hz, CH=CHCOOEt), 7.53 (d, 1H, $J$=8.5 Hz, Ar-H), 6.94 (d, 1H, $J$=2.5 Hz, Ar-H), 6.81 (dd, 1H, $J$=8.5 Hz and 2.5 Hz, Ar-H), 6.24 (d, 1H, $J$=15.8 Hz, CH=CHCOOEt), 4.62 (s, 2H, Ar-CH$_2$OCH$_2$), 4.23 (q, 2H, $J$=7.3 Hz, OCH$_2$CH$_3$), 4.13 (q, 2H, $J$=7.3 Hz, OCH$_2$CH$_3$), 3.81 (s, 3H, Ar-CH$_3$), 3.79 (t, 2H, $J$=6.5 Hz, OCH$_2$CH$_2$COOEt), 2.61 (t, 2H, $J$=6.5 Hz, OCH$_2$CH$_2$COOEt), 1.31 (t, 3H, $J$=7.3 Hz, OCH$_2$CH$_3$), 1.23 (t, 3H, $J$=7.3 Hz, OCH$_2$CH$_3$) ppm.

**$^{13}$C-NMR (CDCl$_3$, 100 MHz):** $\delta$=171.4 (s, O=C–O), 167.1 (s, O=C–O), 161.0 (s, Ar-C), 140.8 (d, CH=CHCOOEt), 139.0 (s, Ar-C), 128.3 (d, Ar-CH), 125.6 (s, Ar-C), 117.5 (d, CH=CHCOOEt), 114.0 (d, Ar-CH), 113.7 (d, Ar-CH), 70.6 (t,
Ar-CH₂OCH₂), 66.0 (t, OCH₂CH₂COOEt), 60.5 (t, OCH₂CH₃), 60.3 (t, OCH₂CH₃), 55.3 (q, Ar-OCH₃), 35.1 (t, OCH₂CH₂COOEt), 14.3 (q, OCH₂CH₃), 14.2 (q, OCH₂CH₃) ppm.

**HR-MS (ESI⁺):** m/z calculated for [C_{18}H_{24}NaO₆]^⁺=[M+Na]^⁺: 359.1465; found 359.1464.

**Ethyl (2E)-3-{4-(benzyloxy)-2-[(3-ethoxy-3-oxopropoxy)methyl]-5-methoxyphenyl}acrylate (23d):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21d (100 mg, 0.31 mmol), ethyl acrylate (155 mg, 1.55 mmol) and Cs₂CO₃ (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (6.8 mg, 10 mol%) and PPh₃ (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the diester 23d (62 mg, 45%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 64–68 °C). [TLC control (petroleum ether/ethyl acetate 70:30), Rf(1d)=0.44, Rf(3ad)=0.44, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νmax=2929, 2871, 1732, 1708, 1631, 1600, 1513, 1456, 1371, 1273, 1169, 1110, 1028, 858, 740, 698 cm⁻¹.

**¹H NMR (CDCl₃, 400 MHz):** δ=7.88 (d, 1H, J=15.8 Hz, CH=CHCOOEt), 7.43 (d, 2H, J=7.2 Hz, Ar-H), 7.36 (d, 1H, J=7.2 Hz, Ar-H), 7.35 (d, 1H, J=7.2 Hz, Ar-H), 7.29 (t, 1H, J=7.2 Hz, Ar-H), 7.09 (s, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.26 (d, 1H, J=15.8 Hz, Ar=CH=CHCOOEt), 5.18 (s, 2H, PhOCH₂Ar), 4.55 (s, 2H, ArCH₂OCH₂), 4.25 (q, 2H, J=7.2 Hz, OCH₂CH₃), 4.13 (q, 2H, J=7.2 Hz, OCH²CH₃), 3.89 (s, 3H, Ar-OCH₃), 3.70 (t, 2H, J=6.5 Hz, OCH₂CH₂COOEt), 2.56 (t, 2H, J=6.5 Hz, OCH₂CH₂COOEt), 1.33 (t, 3H, J=7.2 Hz, OCH₂CH₃), 1.23 (t, 3H, J=7.2 Hz, OCH₂CH₃) ppm.
\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta=171.4\) (s, O=\(\text{C}–\text{O}\)), 167.0 (s, O=\(\text{C}–\text{O}\)), 149.8 (s, Ar-C), 149.2 (s, Ar-C), 140.9 (d, CH=CHCOOEt), 136.6 (s, Ar-C), 130.7 (s, Ar-C), 128.6 (d, 2C, Ar-C), 128.0 (d, Ar-CH), 127.3 (d, 2C, Ar-CH), 126.1 (s, Ar-C), 117.8 (d, Ar-CH), 114.3 (d, Ar-CH), 109.5 (d, CH=CHCOOEt), 70.8 (t, PhCH\(_2\)OAr), 70.1 (t, Ar-CH\(_2\)OCH\(_2\)), 65.7 (t, OCH\(_2\)CH\(_2\)COOEt), 60.5 (t, OCH\(_2\)CH\(_3\)), 60.4 (t, OCH\(_2\)CH\(_3\)), 56.1 (q, Ar-OCH\(_3\)), 35.0 (t, OCH\(_2\)C\(_\text{H}_2\)CH\(_3\)), ppm.

HR-MS (ESI\(^{+}\)): m/z calculated for \([C_{25}\text{H}_{30}\text{NaO}_7]^+=[\text{M+Na}]^+: 465.1884; found 465.1853.

Ethyl \((2E)-3\{5\text{-benzyloxy}\}-2\{\text{3-ethoxy-3-oxopropanoyl}\}\text{methyl}\}4\text{-methoxyphenyl} \text{acrylate} \((23\text{e})\):

GP-2 was carried out with the 2-bromobenzyl alcohol \(21\text{e}\) (100 mg, 0.31 mmol), ethyl acrylate (155 mg, 1.55 mmol) and Cs\(_2\)CO\(_3\) (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)\(_2\) (6.8 mg, 10 mol%) and PPh\(_3\) (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the diester \(23\text{e}\) (64.6 mg, 47%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 64–66 °C). [TLC control (petroleum ether/ethyl acetate 70:30), \(R_f(21\text{e})=0.44, R_f(23\text{e})=0.44\), UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \(\nu_{\text{max}}=2978, 2930, 2870, 1731, 1706, 1630, 1600, 1513, 1460, 1264, 1169, 1110, 1028, 859, 742, 698 \text{ cm}^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta=7.86\) (d, 1H, \(J=15.8\) Hz, CH=CHCOOEt), 7.43 (d, 2H, \(J=7.3\) Hz, Ar-H), 7.36 (d, 1H, \(J=7.3\) Hz, Ar-H), 7.35 (d, 1H, \(J=7.3\) Hz, Ar-H), 7.32 (t, 1H, \(J=7.3\) Hz, Ar-H), 7.11 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.14 (d, 1H, \(J=15.8\) Hz, Ar-CH=CHCOOEt), 5.14 (s, 2H, PhOCH\(_2\)Ar), 4.59 (s, 2H,
ArCH₂OCH₂), 4.24 (q, 2H, J=7.3 Hz, OCH₂CH₃), 4.13 (q, 2H, J=7.3 Hz, OCH₂CH₃), 3.91 (s, 3H, Ar-OCH₃), 3.78 (t, 2H, J=6.5 Hz, OCH₂CH₂COOEt), 2.61 (t, 2H, J=6.5 Hz, OCH₂CH₂COOEt), 1.32 (t, 3H, J=7.3 Hz, OCH₂CH₃), 1.23 (t, 3H, J=7.3 Hz, OCH₂CH₃) ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=171.4 (s, O=CH), 167.1 (s, O=CH), 151.3 (s, Ar-C), 147.7 (s, Ar-C), 140.9 (d, CH=CHCOOEt), 136.6 (s, Ar-C), 131.3 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.3 (d, 2C, Ar-CH), 125.6 (s, Ar-C), 117.6 (d, Ar-CH), 112.4 (d, Ar-CH), 111.7 (d, CH=CHCOOEt), 71.1 (t, PhCH₂OAr), 70.2 (t, Ar-CH₂OCH₂), 65.9 (t, OCH₂CH₂COOEt), 60.5 (t, OCH₂CH₃), 60.4 (t, OCH₂CH₃), 56.0 (q, Ar-OCH₃), 35.0 (t, OCH₂CH₂COOEt), 14.3 (q, OCH₂CH₃), 14.1 (q, OCH₂CH₃) ppm.

HR-MS (ESI⁺): m/z calculated for [C₂₅H₃₀NaO₇]⁺=[M+Na]⁺: 465.1884; found 465.1881.

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Ethyl (2E)-3-{6-[1-(3-ethoxy-3-oxopropoxy)methyl]-1,3-benzodioxol-5-yl}acrylate (23f):

GP-2 was carried out with the 2-bromobenzyl alcohol 21f (100 mg, 0.43 mmol), ethyl acrylate (217 mg, 2.16 mmol) and Cs₂CO₃ (282 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (9.7 mg, 10 mol%) and PPh₃ (23 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester 23f (70.5 mg, 46%) as a colourless semi-solid. [TLC control (petroleum ether/ethyl acetate 80:20), Rf(21f)=0.45, Rf(23f)=0.45, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νmax=2981, 2904, 1731, 1709, 1632, 1612, 1504, 1485, 1372, 1293, 1259, 1178, 1037, 931, 858 cm⁻¹.
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$=7.87 (d, 1H, $J$=15.7 Hz, CH=CHCOOEt), 7.05 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 6.22 (d, 1H, $J$=15.7 Hz, CH=CHCOOEt), 5.98 (s, 2H, O-CH$_2$-O), 4.56 (s, 2H, Ar-CH$_2$OCH$_2$), 4.24 (q, 2H, $J$=7.2 Hz, OCH$_2$CH$_3$), 4.14 (q, 2H, $J$=7.2 Hz, OC$_2$H$_5$CH$_3$), 3.77 (t, 2H, OCH$_2$COOEt), 2.61 (t, 2H, $J$=6.5 Hz, OCH$_2$CH$_3$), 1.32 (t, 3H, $J$=7.2 Hz, OCH$_2$CH$_3$), 1.24 (t, 3H, $J$=7.2 Hz, OCH$_2$CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$=171.4 (s, O=C-), 167.0 (s, O=C-), 149.2 (s, Ar-C), 147.7 (s, Ar-C), 140.7 (d, CH=CHCOOEt), 132.4 (s, Ar-C), 127.2 (s, Ar-C), 118.0 (d, CH=CHCOOEt), 109.4 (d, Ar-CH), 105.9 (d, Ar-CH), 101.5 (t, O-CH$_2$-O), 70.2 (t, Ar-CH$_2$OCH$_2$), 65.8 (t, OCH$_2$CH$_2$COOEt), 60.5 (t, OCH$_2$CH$_3$), 60.4 (t, OCH$_2$CH$_3$), 35.0 (t, OCH$_2$CH$_2$COOEt), 14.3 (q, OCH$_2$CH$_3$), 14.1 (q, OCH$_2$CH$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{18}$H$_{22}$NaO$_7$]$^+=[M+Na]$^+$: 373.1258; found 373.1243.

Ethyl (2E)-3-[2-[(3-ethoxy-3-oxopropoxy)methyl]-4,5-dimethoxyphenyl]acrylate (23g):

GP-2 was carried out with the 2-bromobenzyl alcohol 21g (100 mg, 0.40 mmol), ethyl acrylate (203 mg, 2.02 mmol) and Cs$_2$CO$_3$ (264 mg, 0.81 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)$_2$ (9.1 mg, 10 mol%) and PPh$_3$ (21.2 mg, 0.81 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the diester 23g (79 mg, 53%) as a pale brown viscous oil. [TLC control (petroleum ether/ethyl acetate 70:30), $R_f$(21g)=0.40, $R_f$(23g)=0.40, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=2979, 2937, 2868, 1730, 1705, 1630, 1600, 1514, 1464, 1369, 1270, 1165, 1107, 1030, 856 cm$^{-1}$. 

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**1H-NMR (CDCl₃, 400 MHz):** $\delta=7.89$ (d, 1H, $J=15.8$ Hz, CH=CHCOOEt), 7.05 (s, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 6.25 (d, 1H, $J=15.8$ Hz, CH=CHCOOEt), 4.59 (s, 2H, Ar-CH₂OCH₂), 4.23 (q, 2H, $J=7.1$ Hz, OCH₂CH₃), 4.11 (q, 2H, $J=7.1$ Hz, OCH₂CH₃), 3.89 (s, 3H, Ar-OCH₃), 3.87 (s, 3H, Ar-OCH₃), 3.77 (t, 2H, $J=6.4$ Hz, OCH₂CH₂COOEt), 2.60 (t, 2H, $J=6.4$ Hz, OCH₂CH₂COOEt), 1.31 (t, 3H, $J=7.1$ Hz, OCH₂CH₃), 1.25 (t, 3H, $J=7.1$ Hz, OCH₂CH₃) ppm.

**13C-NMR (CDCl₃, 100 MHz):** $\delta=171.4$ (s, O=C=O), 167.0 (s, O=C=O), 150.7 (s, Ar-C), 148.7 (s, Ar-C), 140.9 (d, CH=CHCOOEt), 130.9 (s, Ar-C), 125.7 (s, Ar-C), 117.7 (d, Ar-CH), 112.1 (d, Ar-CH), 109.0 (d, CH=CHCOOEt), 70.2 (t, Ar-CH₂OCH₂), 65.8 (t, OCH₂CH₂COOEt), 60.5 (t, OCH₂CH₃), 60.4 (t, OCH₂CH₃), 56.0 (q, 2C, 2 × Ar-OCH₃), 35.1 (t, OCH₂CH₂COOEt), 14.3 (q, OCH₂CH₃), 14.1 (q, OCH₂CH₃) ppm.

**HR-MS (ESI⁺):** m/z calculated for [C₁₉H₂₇O₇]+= [M+H]⁺: 367.1751; found 367.1748.

![Chemical Structure](image)

**Ethyl (2E)-3-{6-[(3-ethoxy-3-oxopropoxy)methyl]-2,3,4-trimethoxyphenyl}acrylate (23h):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21h (100 mg, 0.36 mmol), ethyl acrylate (180.7 mg, 1.80 mmol) and Cs₂CO₃ (235 mg, 0.72 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (8.1 mg, 10 mol%) and PPh₃ (19.0 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester 23h (77 mg, 51%) as a colorless viscous oil. [TLC control (petroleum ether/ethyl acetate 80:25), $R_f(21h)=0.45$, $R_f(23h)=0.45$, UV detection].
IR (neat; MIR-ATR, 4000–600 cm⁻¹); \( \nu_{\text{max}} = 2980, 2938, 1734, 1711, 1630, 1591, 1461, 1300, 1176, 1129, 1031, 987 \) cm⁻¹.

\(^1\)H-NMR (CDCl₃, 400 MHz): \( \delta = 7.76 \) (d, 1H, \( J = 16.2 \) Hz, \( \text{CH} = \text{CH}_2 \text{COOEt} \)), 6.81 (s, 1H, Ar-H), 6.50 (d, 1H, \( J = 16.2 \) Hz, \( \text{CH} = \text{CHCOOEt} \)), 4.54 (s, 2H, Ar-CH₂OCH₂), 4.25 (q, 2H, \( J = 7.1 \) Hz, OCH₂CH₃), 3.89 (s, 3H, Ar-OCH₃), 3.85 (s, 6H, 2 × Ar-OCH₃), 3.81 (t, 2H, \( J = 6.4 \) Hz, OCH₂CH₂COOEt), 2.64 (t, 2H, \( J = 6.4 \) Hz, OCH₂CH₂COOEt), 1.32 (t, 3H, \( J = 7.1 \) Hz, OCH₂CH₃), 1.24 (t, 3H, \( J = 7.1 \) Hz, OCH₂CH₃) ppm.

\(^{13}\)C-NMR (CDCl₃, 100 MHz): \( \delta = 171.5 \) (s, O=C–O), 167.8 (s, O=C–O), 154.2 (s, Ar-C), 153.6 (s, Ar-C), 141.8 (s, Ar-C), 137.6 (d, CH=CHCOOEt), 133.6 (s, Ar-C), 121.5 (d, Ar-CH), 120.4 (s, Ar-C), 108.3 (d, CH=CHCOOEt), 71.1 (t, Ar-CH₂OCH₂), 66.0 (t, OCH₂CH₂COOEt), 60.9 (q, Ar-OCH₃), 60.7 (q, Ar-OCH₃), 60.5 (t, OCH₂CH₃), 60.3 (t, OCH₂CH₃), 56.0 (q, Ar-OCH₃), 35.0 (t, OCH₂CH₂COOEt), 14.3 (q, OCH₂CH₃), 14.2 (q, OCH₂CH₃) ppm.

HR-MS (ESI⁺): m/z calculated for \([\text{C}_{20}\text{H}_{28}\text{NaO}_8]^+\)=[M+Na]⁺: 419.1676; found 419.1676.

![Ethyl (2E)-3-[2-[1-(3-ethoxy-3-oxopropoxy)ethyl]-4,5-dimethoxyphenyl]acrylate (23i):](image)

GP-2 was carried out with the 2-bromobenzyl alcohol 21o (100 mg, 0.38 mmol), ethyl acrylate (192 mg, 1.91 mmol) and Cs₂CO₃ (250 mg, 0.77 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (8.6 mg, 10 mol%) and PPh₃ (20.1 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the diester 23i (48 mg,
33%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 70:30), \(R_f(21b) = 0.45\), \(R_f(23i) = 0.45\), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \(\nu_{\text{max}} = 2977, 2934, 1732, 1708, 1601, 1510, 1464, 1263, 1168, 1098, 1028, 862\) cm\(^{-1}\).

**\(^1\)H-NMR (CDCl\(_3\), 400 MHz)**: \(\delta = 7.97\) (d, 1H, \(J=15.7\) Hz, CH=CHCOOEt), 7.01 (s, 1H, Ar-H), 7.01 (s, 1H, Ar-H), 6.25 (d, 1H, \(J=15.7\) Hz, CH=CHCOOEt), 4.83 [q, 1H, \(J=6.4\) Hz, Ar-CH(CH\(_3\))OCH\(_2\)], 4.26 (q, 2H, \(J=7.1\) Hz, OCH\(_2\)CH\(_3\)), 4.13 (dq, 2H, \(J=7.1\) and 2.4 Hz OCH\(_2\)CH\(_3\)), 3.93 (s, 3H, Ar-OCH\(_3\)), 3.89 (s, 3H, Ar-OCH\(_3\)), 3.59 (ddd, 1H, \(J=12.9, 9.4\) and 6.1 Hz, OCH\(_2\)CH\(_2\)COOEt), 3.56 (ddd, 1H, \(J=12.9, 9.4\) and 6.1 Hz, OCH\(_2\)CH\(_2\)COOEt), 2.56 (dd, 1H, \(J=6.1\) and 2.7 Hz, OCH\(_2\)CH\(_2\)COOEt), 2.55 (dd, 1H, \(J=6.1\) and 2.7 Hz, OCH\(_2\)CH\(_2\)COOEt), 1.38 [d, 3H, \(J=6.4\), Ar-CH(CH\(_3\))OCH\(_2\)], 1.34 (t, 3H, \(J=7.1\) Hz, OCH\(_2\)CH\(_3\)), 1.24 (t, 3H, \(J=7.1\) Hz, OCH\(_2\)CH\(_3\)) ppm.

**\(^{13}\)C NMR (CDCl\(_3\), 100 MHz)**: \(\delta = 171.5\) (s, O=C–O), 167.1 (s, O=C–O), 151.4 (s, Ar-C), 148.2 (s, Ar-C), 140.4 (d, CH=CHCOOEt), 137.0 (s, Ar-C), 124.3 (s, Ar-C), 117.7 (d, CH=CHCOOEt), 108.5 (d, Ar-CH), 108.4 (d, Ar-CH), 74.1 [d, Ar-CH(CH\(_3\))OCH\(_2\)], 64.2 (t, OCH\(_2\)CH\(_2\)COOEt), 60.5 (t, OCH\(_2\)CH\(_3\)), 60.4 (t, OCH\(_2\)CH\(_3\)), 56.0 (q, Ar-OCH\(_3\)), 55.9 (q, Ar-OCH\(_3\)), 35.2 (q, OCH\(_2\)CH\(_2\)COOEt), 24.2 [q, Ar-CH(CH\(_3\))OCH\(_2\)], 14.3 (q, OCH\(_2\)CH\(_3\)), 14.2 (q, OCH\(_2\)CH\(_3\)) ppm.

**HR-MS (ESI\(^{+}\))**: m/z calculated for [C\(_{20}\)H\(_{29}\)O\(_7\)]\(^{+}\)=[M+H]\(^{+}\): 381.1908; found 381.1900.

![Tert-butyl (2E)-3-{2-[(3-tert-butoxy-3-oxopropoxy)methyl]phenyl}acrylate (23j)](image)

**Tert-butyl (2E)-3-{2-[(3-tert-butoxy-3-oxopropoxy)methyl]phenyl}acrylate (23j):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21a (100 mg, 0.53 mmol), tertiarybutyl acrylate (342 mg, 2.67 mmol) and Cs\(_2\)CO\(_3\) (348.5 mg, 1.07 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)\(_2\) (12 mg, 10 mol%) and PPh\(_3\) (28
mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 90:10) furnished the diester \(23j\) (138.3 mg, 71%) as a colourless viscous oil. [TLC control (petroleum ether/ethyl acetate 90:10), \(R_f(21a)=0.40, R_f(23j)=0.55\), UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \(\nu_{max}=2977, 1726, 1709, 1633, 1602, 1367, 1150, 912, 846, 732\) cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta=7.86\) (d, 1H, \(J=15.8\) Hz, CH=CHCOO\(t\)Bu), 7.56 (dd, 1H, \(J=7.3\) and 1.1 Hz, Ar-H), 7.39 (dd, 1H, \(J=7.4\) and 1.5 Hz, Ar-H), 7.31 (ddd, 1H, \(J=8.5, 7.4\) and 1.5 Hz, Ar-H), 7.29 (ddd, 1H, \(J=8.5, 7.3\) and 1.1 Hz, Ar-H), 6.29 (d, 1H, \(J=15.8\) Hz, CH=CHCOO\(t\)Bu), 4.62 (s, 2H, Ar-CH\(_2\)OCH\(_2\)), 3.75 (t, 2H, \(J=6.6\) Hz, OCH\(_2\)CH\(_2\)COO\(t\)Bu), 2.54 (t, 2H, \(J=6.6\) Hz, OCH\(_2\)CH\(_2\)COO\(t\)Bu), 1.53 [s, 9H, OC(CH\(_3\))\(_3\)], 1.43 [s, 9H, OC(CH\(_3\))\(_3\)] ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta=170.8\) (s, O=C–O), 166.2 (s, O=C–O), 140.4 (d, CH=CHCOO\(t\)Bu), 136.9 (s, Ar-C), 133.6 (s, Ar-C), 129.6 (d, Ar-CH), 129.1 (d, Ar-CH), 128.1 (d, Ar-CH), 126.6 (d, Ar-CH), 122.0 (d, CH=CHCOO\(t\)Bu), 80.6 [s, OC(CH\(_3\))\(_3\)], 80.5 [s, OC(CH\(_3\))\(_3\)], 70.7 (t, Ar-CH\(_2\)OCH\(_2\)), 66.3 (t, OCH\(_2\)CH\(_2\)COO\(t\)Bu), 36.3 (t, CH\(_2\)CH\(_2\)COO\(t\)Bu), 28.2 [q, 3C, OC(CH\(_3\))\(_3\)], 28.1 [q, 3C, OC(CH\(_3\))\(_3\)] ppm.

HR-MS (ESI\(^{+}\)): m/z calculated for [C\(_{21}\)H\(_{30}\)NaO\(_5\)]\(^+\)=[M+Na]\(^+\): 385.1985; found 385.1984.

**Tert-butyl (2E)-3-[4-(benzyloxy)-2-{(3-tert-butoxy-3-oxopropoxy)methyl}phenyl]acrylate (23k):**

GP-2 was carried out with the 2-bromobenzyl alcohol \(21b\) (100 mg, 0.36 mmol), tertiarybutyl acrylate (229.4 mg, 1.79 mmol) and Cs\(_2\)CO\(_3\) (234 mg, 0.72 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)\(_2\) (8 mg, 10 mol%) and PPh\(_3\) (19
mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to 85:15) furnished the diester 23k (136.4 mg, 84%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), Rf(21b)=0.45, Rf(23k)=0.60, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νmax=2975, 2926, 1728, 1705, 1628, 1590, 1458, 1366, 1304, 1243, 1153, 1130, 986, 848 cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** δ=7.78 (d, 1H, J=15.8 Hz, CH=CHCOOᵗBu), 7.53 (d, 1H, J=8.5 Hz, Ar-H), 7.46–7.26 (m, 5H, Ar-H), 7.07 (d, 1H, J=2.6 Hz, Ar-H), 6.87 (dd, 1H, J=8.5 and 2.6 Hz, Ar-H), 6.19 (d, 1H, J=15.8 Hz, CH=CHCOOᵗBu), 5.08 (s, 2H, Ar-OCH₂Ph), 4.62 (s, 2H, Ar-CH₂OCH₂), 3.75 (t, 2H, J=6.5 Hz, OCH₂CH₂COOᵗBu), 2.54 (t, 2H, J=6.5 Hz, OCH₂CH₂COOᵗBu), 1.52 [s, 9H, OC(CH₃)₃], 1.44 [s, 9H, OC(CH₃)₃] ppm.

**¹³C NMR (CDCl₃, 100 MHz):** δ=170.7 (s, O=C−O), 166.5 (s, O=C−O), 160.1 (s, Ar-C), 139.7 (d, CH=CHCOOᵗBu), 139.0 (s, Ar-C), 136.6 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.2 (d, Ar-CH), 128.0 (d, Ar-CH), 127.5 (d, 2C, Ar-CH), 125.8 (s, Ar-C), 119.6 (d, CH=CHCOOᵗBu), 114.6 (d, Ar-CH), 114.5 (d, Ar-CH), 80.6 [s, OC(CH₃)₃], 80.3 [s, OC(CH₃)₃], 70.4 (t, Ar-OCH₂Ph), 70.0 (t, Ar-CH₂OCH₂), 66.3 (t, OCH₂CH₂COOᵗBu), 36.2 (t, OCH₂CH₂COOᵗBu), 28.2 [q, 3C, OC(CH₃)₃], 28.1 [q, 3C, OC(CH₃)₃] ppm.

**HR-MS (ESI⁺):** m/z calculated for [C₂₈H₃₆NaO₆]+=[M+Na]⁺: 491.2404; found 491.2395.

\[\text{Tert-butyl (2E)-3-[2-[(3-tert-butoxy-3-oxopropoxy)methyl]-4-methoxyphenyl]acrylate (23l):}\]

GP-2 was carried out with the 2-bromobenzyl alcohol 21c (100 mg, 0.46 mmol), tertiarybutyl acrylate (295 mg, 2.30 mmol) and Cs₂CO₃ (300 mg, 0.92 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction
mixture at room temperature, were added Pd(OAc)$_2$ (10.3 mg, 10 mol%) and PPh$_3$ (24.2 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester 23l (140.2 mg, 78%) as a colorless viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), $R_f$(21c)=0.43, $R_f$(23l)=0.58, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{max}$=2976, 2933, 1727, 1704, 1630, 1603, 1497, 1366, 1255, 1145, 980, 864 cm$^{-1}$.

**$^1$H-NMR (CDCl$_3$, 400 MHz):** $\delta$=7.77 (d, 1H, $J$=15.8 Hz, CH=CHCOO$^t$Bu), 7.52 (d, 1H, $J$=8.6 Hz, Ar-H), 6.96 (d, 1H, $J$=2.6 Hz, Ar-H), 6.80 (dd, 1H, $J$=8.6 and 2.6 Hz, Ar-H), 6.19 (d, 1H, $J$=15.8 Hz, CH=CHOO$^t$Bu), 4.61 (s, 2H, Ar-CH$_2$OCH$_2$), 3.82 (s, 3H, Ar-OCH$_3$), 3.76 (t, 2H, $J$=6.5 Hz, OCH$_2$CH$_2$COO$^t$Bu), 2.55 (t, 2H, $J$=6.5 Hz, OCH$_2$CH$_2$COO$^t$Bu), 1.52 [s, 9H, OC(CH$_3$)$_3$], 1.43 [s, 9H, OC(CH$_3$)$_3$] ppm.

**$^{13}$C-NMR (CDCl$_3$, 100 MHz):** $\delta$=170.7 (s, O=C=O), 166.5 (s, O=C=O), 160.9 (s, Ar-C), 139.8 (d, CH=CHCOO$^t$Bu), 139.0 (s, Ar-C), 128.1 (d, Ar-CH), 125.6 (s, Ar-C), 119.4 (d, CH=CHCOO$^t$Bu), 113.8 (d, Ar-CH), 113.7 (d, Ar-CH), 80.6 [s, OC(CH$_3$)$_3$], 80.2 [s, OC(CH$_3$)$_3$], 70.5 (t, Ar-CH$_2$OCH$_2$), 66.3 (t, OCH$_2$CH$_2$COO$^t$Bu), 55.3 (q, Ar-OCH$_3$), 36.2 (t, OCH$_2$CH$_2$COO$^t$Bu), 28.2 [q, 3C, OC(CH$_3$)$_3$], 28.1 [q, 3C, OC(CH$_3$)$_3$] ppm.

**HR-MS (ESI$^+$) m/z calculated for [C$_{22}$H$_{32}$NaO$_6$]$^+$=[M+Na]$^+$: 415.2091; found 415.2082.

**Ter$^t$-butyl (2E)-3-[4-(benzzyloxy)-2-[(3-tert-butoxy-3-oxopropoxymethyl]-5-methoxyphenyl]acrylate (23m):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21d (100 mg, 0.31 mmol), tertiarybutyl acrylate (199 mg, 1.55 mmol) and Cs$_2$CO$_3$ (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction
mixture at room temperature, were added Pd(OAc)$_2$ (6.8 mg, 10 mol%) and PPh$_3$ (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 75:25) furnished the diester 23m (110 mg, 71%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 76–80 °C). [TLC control (petroleum ether/ethyl acetate 70:30), $R_f$(21d)=0.44, $R_f$(23m)=0.60, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{\text{max}}$=2978, 2930, 2871, 1729, 1703, 1632, 1600, 1516, 1384, 1367, 1277, 1152, 1110, 1028, 855, 741 cm$^{-1}$.

**$^1$H-NMR (CDCl$_3$, 400 MHz):** $\delta$=7.80 (d, 1H, $J$=15.8 Hz, CH=CHCOO$^{t}$Bu), 7.43 (d, 2H, $J$=7.2 Hz, Ar-H), 7.35 (d, 1H, $J$=7.2 Hz, Ar-H), 7.34 (d, 1H, $J$=7.2 Hz, Ar-H), 7.29 (t, 1H, $J$=7.2 Hz, Ar-H), 7.08 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 6.20 (d, 1H, $J$=15.8 Hz, Ar-CH=CHCOO$^{t}$Bu), 5.16 (s, 2H, PhCH$_2$OAr), 4.54 (s, 2H, ArCH$_2$OCH$_2$), 3.88 (s, 3H, Ar-OCH$_3$), 3.67 (t, 2H, $J$=6.5 Hz, OCH$_2$CH$_2$COO$^{t}$Bu), 2.49 (t, 2H, $J$=6.5 Hz, OCH$_2$CH$_2$COO$^{t}$Bu), 1.53 [s, 9H, OC(CH$_3$)$_3$], 1.43 [s, 9H, OC(CH$_3$)$_3$] ppm.

**$^{13}$C-NMR (CDCl$_3$, 100 MHz):** $\delta$=170.7 (s, O=C=O), 166.3 (s, O=C=O), 149.6 (s, Ar-C), 149.0 (s, Ar-C), 139.9 (d, CH=CHCOO$^{t}$Bu), 136.6 (s, Ar-C), 130.7 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.3 (d, 2C, 2 $\times$ Ar-CH), 126.1 (s, Ar-C), 119.5 (d, Ar-CH), 114.1 (d, Ar-CH), 109.4 (d, CH=CHCOO$^{t}$Bu), 80.5 [s, OC(CH$_3$)$_3$], 80.3 [s, OC(CH$_3$)$_3$], 70.8 (t, PhCH$_2$OAr), 70.0 (t, Ar-CH$_2$OCH$_2$), 66.0 (t, OCH$_2$CH$_2$COO$^{t}$Bu), 56.0 (q, Ar-OCH$_3$), 36.1 (t, OCH$_2$CH$_2$COO$^{t}$Bu), 28.2 [q, 3C, OC(CH$_3$)$_3$], 28.0 [q, 3C, OC(CH$_3$)$_3$] ppm.

**HR-MS (ESI$^+$):** m/z calculated for [C$_{29}$H$_{38}$NaO$_7$]$^+$=[M+Na]$^+$: 525.2510; found 521.2506.

![23n](image)

**Tert-butyl (2E)-3-[5-(benzyloxy)-2-[(3-tert-butoxy-3-oxopropoxy)methyl]-4-methoxyphenyl]acrylate (23n):**
GP-2 was carried out with the 2-bromobenzyl alcohol 21e (100 mg, 0.31 mmol), tertiarybutyl acrylate (199 mg, 1.55 mmol) and Cs$_2$CO$_3$ (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)$_2$ (6.8 mg, 10 mol%) and PPh$_3$ (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 75:25) furnished the diester 23n (140 mg, 90%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 77–79 °C). [TLC control (petroleum ether/ethyl acetate 70:30), $R_f$ (21e)=0.44, $R_f$ (23n)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)):
\[ \nu_{max} = 2975, 2927, 2869, 1727, 1704, 1630, 1600, 1513, 1366, 1278, 1150, 1112, 979, 851 \text{ cm}^{-1} \].

$^1$H-NMR (CDCl$_3$, 400 MHz):
\[ \delta = 7.77 \text{ (d, 1H, } J=15.8 \text{ Hz, } CH=\text{CHCOO'Bu}) , 7.43 \text{ (d, 2H, } J=7.2 \text{ Hz, Ar-H}), 7.37 \text{ (d, 1H, } J=7.2 \text{ Hz, Ar-H}), 7.35 \text{ (d, 1H, } J=7.2 \text{ Hz, Ar-H}), 7.30 \text{ (t, 1H, } J=7.2 \text{ Hz, Ar-H}), 7.11 \text{ (s, 1H, Ar-H)}, 6.95 \text{ (s, 1H, Ar-H)}, 6.08 \text{ (d, 1H, } J=15.8 \text{ Hz, Ar-CH=CHCOO'Bu}), 5.13 \text{ (s, 2H, PhCH$_2$OAr}), 4.58 \text{ (s, 2H, ArCH$_2$OCH$_2$), 3.90 \text{ (s, 3H, Ar-OCH$_3$), 3.75 \text{ (t, 2H, } J=6.5 \text{ Hz, OCH$_2$CH$_2$COO'Bu}), 2.54 \text{ (t, 2H, } J=6.5 \text{ Hz, OCH$_2$CH$_2$COO'Bu}), 1.52 \text{ [s, 9H, OC(CH$_3$)$_3$], 1.43 \text{ [s, 9H, OC(CH$_3$)$_3$]} }} \text{ ppm.} \]

$^{13}$C-NMR (CDCl$_3$, 100 MHz):
\[ \delta = 170.7 \text{ (s, O=C–O), 166.4 \text{ (s, O=C–O), 151.2 \text{ (s, Ar-C), 147.7 \text{ (s, Ar-C), 139.8 \text{ (d, CH=CHCOO'Bu), 136.7 \text{ (s, Ar-C), 131.3 \text{ (s, Ar-C), 128.6 \text{ (d, 2C, Ar–CH), 128.0 \text{ (d, Ar–CH), 127.4 \text{ (d, 2C, Ar–CH), 125.6 \text{ (s, Ar–C), 119.5 \text{ (d, Ar-CH), 112.3 \text{ (d, Ar-CH), 111.8 \text{ (d, CH=CHCOO'Bu), 80.5 \text{ [s, OC(CH$_3$)$_3$]}, 80.3 \text{ [s, OC(CH$_3$)$_3$]}, 71.2 \text{ (t, PhCH$_2$OAr), 70.1 \text{ (t, Ar-CH$_2$OCH$_2$), 66.2 \text{ (t, OCH$_2$CH$_2$COO'Bu), 56.0 \text{ (q, Ar-OCH$_3$), 36.2 \text{ (t, OCH$_2$CH$_2$Bu)}, 28.2 \text{ [q, 3C, OC(CH$_3$)$_3$], 28.1 \text{ [q, 3C,OC(CH$_3$)$_3$]} }} \text{ ppm.} \]

HR-MS (ESI$^+$):
\[ m/z \text{ calculated for } [C_{29}H_{38}NaO_7]^+=[M+Na]^+: 521.2510; \text{ found 521.2500.} \]
**Tert-butyl (2E)-3-{6-[3-tert-butoxy-3-oxopropoxy)methyl]-1,3-benzodioxol-5-yl]acrylate (23o):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21f (100 mg, 0.43 mmol), tertiarybutyl acrylate (277 mg, 2.16 mmol) and Cs₂CO₃ (282 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (9.7 mg, 10 mol%) and PPh₃ (23 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester 23o (144.4 mg, 87%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), \( R_f(21f)=0.45, R_f(23o)=0.60 \), UV detection].

**IR** (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{max}=2976, 1728, 1705, 1630, 1602, 1483, 1366, 1293, 1256, 1151, 1039, 849 \) cm⁻¹.

**¹H-NMR** (CDCl₃, 400 MHz): \( \delta=7.77 \) (d, 1H, \( J=15.7 \) Hz, \( CH=CHCOO'Bu \)), 7.03 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 6.14 (d, 1H, \( J=15.7 \) Hz, \( CH=CHCOO'Bu \)), 5.96 (s, 2H, O-CH₂-O), 4.54 (s, 2H, Ar-CH₂OCH₂), 3.73 (t, 2H, \( J=6.5 \) Hz, OCH₂CH₂COO'Bu), 2.52 (t, 2H, \( J=6.5 \) Hz, OCH₂CH₂COO'Bu), 1.51 [s, 9H, OC(CH₃)₃], 1.43 [s, 9H, OC(CH₃)₃] ppm.

**¹³C-NMR** (CDCl₃, 100 MHz): \( \delta=170.7 \) (s, O=O-C), 166.4 (s, O=C-O), 149.1 (s, Ar-C), 147.6 (s, Ar-C), 139.7 (d, CH=CHCOO'Bu), 132.4 (s, Ar-C), 127.2 (s, Ar-C), 119.8 (d, CH=CHCOO'Bu), 109.3 (d, Ar-CH), 105.8 (d, Ar-CH), 101.4 (t, O-CH₂-O), 80.6 [s, OC(CH₃)₃], 80.4 [s, OC(CH₃)₃], 70.1 (t, Ar-CH₂OCH₂), 66.2 (t, OCH₂CH₂COO'Bu), 36.2 (t, OCH₂CH₂COO'Bu), 28.2 [q, 3C, OC(CH₃)₃], 28.0 [q, 3C, OC(CH₃)₃] ppm.

**HR-MS** (ESI⁺): \( m/z \) calculated for \([C_{22}H_{30}NaO_{7}]^+=[M+Na]^+\): 429.1884; found 429.1882.
**Tert-butyl (2E)-3-[2-[(3-tert-butoxy-3-oxopropoxy)methyl]-4,5-dimethoxyphenyl]acrylate (23p):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21g (100 mg, 0.40 mmol), tertiarybutyl acrylate (260 mg, 2.02 mmol) and Cs₂CO₃ (264 mg, 0.81 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture, were added Pd(OAc)₂ (9.1 mg, 10 mol%) and PPh₃ (21.2 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester 23p (122.4 mg, 72%) as a pale brown viscous oil. [TLC control (petroleum ether/ethyl acetate 70:30), Rₖ(21g)=0.40, Rₖ(23p)=0.58, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νₘₐₓ=2976, 2933, 1728, 1704, 1602, 1515, 1366, 1277, 1148, 1110, 849 cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** δ=7.82 (d, 1H, J=15.7 Hz, CH=CHO₂Bu), 7.06 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.19 (d, 1H, J=15.7 Hz, CH=CHO₂Bu), 4.59 (s, 2H, Ar-CH₂OCH₂), 3.90 (s, 3H, Ar-OCH₃), 3.89 (s, 3H, Ar-OCH₃), 3.75 (t, 2H, J=6.5 Hz, OCH₂CH₂COO₂Bu), 2.54 (t, 2H, J=6.5 Hz, OCH₂CH₂COO₂Bu), 1.53 [s, 9H, OC(CH₃)₃], 1.43 [s, 9H, OC(CH₃)₃] ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** δ=170.8 (s, O=C–O), 166.4 (s, O=C–O), 150.5 (s, Ar-C), 148.5 (s, Ar-C), 139.9 (d, CH=CHO₂Bu), 130.9 (s, Ar-C), 125.7 (s, Ar-C), 119.4 (d, CH=CHO₂Bu), 111.8 (d, Ar-CH), 108.7 (d, Ar-CH), 80.6 [s, OC(CH₃)₃], 80.4 [s, OC(CH₃)₃], 70.1 (t, Ar-CH₂OCH₂), 66.2 (t, OCH₂CH₂COO₂Bu), 55.9 (2 × q, 2C, 2 × Ar-OCH₃), 36.2 (t, OCH₂CH₂COO₂Bu), 28.2 [q, 3C, OC(CH₃)₃], 28.1 [q, 3C, OC(CH₃)₃] ppm.

**HR-MS (ESI⁺):** m/z calculated for [C₂₃H₃₄NaO₇]⁺=[M+Na]⁺: 445.2197; found 445.2191.
**Tert-butyl (2E)-3-[(3-tert-butoxy-3-oxopropoxy)methyl]-2,3,4-trimethoxyphenyl]acrylate (23q):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21h (100 mg, 0.36 mmol), tertiarybutyl acrylate (231 mg, 1.80 mmol) and Cs₂CO₃ (235 mg, 0.72 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (8.1 mg, 10 mol%) and PPh₃ (19 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester 23q (129.4 mg, 79%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R₉(21h)=0.45, R₉(23q)=0.60, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** ν_max=2974, 2921, 2851, 1728, 1705, 1591, 1458, 1366, 1330, 1304, 1243, 1152, 1128, 986, 848 cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** δ=7.67 (d, 1H, J=16.2 Hz, CH=CHCOO' Bu), 6.83 (s, 1H, Ar-H), 6.40 (d, 1H, J=16.2 Hz, CH=CHCOO' Bu), 4.54 (s, 2H, Ar-CH₂OCH₂), 3.88 (s, 3H, Ar-OCH₃), 3.85 (s, 6H, 2 x Ar-OCH₃), 3.77 (t, 2H, J=6.5 Hz, OCH₂CH₂COO' Bu), 2.56 (t, 2H, J=6.5 Hz, OCH₂CH₂COO' Bu), 1.52 [s, 9H, OC(CH₃)₃], 1.43 [s, 9H, OC(CH₃)₃] ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** δ=170.8 (s, O=C=O), 167.1 (s, O=C=O), 154.0 (s, Ar-C), 153.4 (s, Ar-C), 141.7 (s, Ar-C), 136.5 (d, CH=CHCOO' Bu), 133.6 (s, Ar-C), 123.4 (d, CH=CHCOO' Bu), 120.4 (s, Ar-C), 108.1 (d, Ar-CH), 80.6 [s, OC(CH₃)₃], 80.1 [s, OC(CH₃)₃], 71.0 (t, Ar-CH₂OCH₂), 66.3 (t, OCH₂CH₂COO' Bu), 60.8 (q, Ar-OCH₃), 60.7 (q, Ar-OCH₃), 55.9 (q, Ar-OCH₃), 36.2 (t, OCH₂CH₂COO' Bu), 28.2 [q, 3C, OC(CH₃)₃], 28.1 [q, 3C, OC(CH₃)₃] ppm.

**HR-MS (ESI⁺):** m/z calculated for [C₂₄H₃₆NaO₈]⁺=[M+Na]⁺: 475.2302; found 475.2285.
**Tert-butyl (2E)-3-[2-[(3-tert-butoxy-3-oxopropoxy)methyl]-4-nitrophenyl]acrylate (23r):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21i (100 mg, 0.43 mmol), tertiarybutyl acrylate (276 mg, 2.15 mmol) and Cs₂CO₃ (281 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (9.6 mg, 10 mol%) and PPh₃ (22.6 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester 23r (129.8 mg, 74%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), \( R_f(21i)=0.30, R_f(23r)=0.65 \), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** \( \nu_{\text{max}}=2978, 1714, 1524, 1367, 1347, 1324, 1256, 1154, 1070, 980, 846 \) cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** \( \delta=8.30 \) (d, 1H, \( J=2.3 \) Hz, Ar-H), 8.12 (dd, 1H, \( J=8.5 \) and 2.3 Hz, Ar-H), 7.77 (d, 1H, \( J=15.8 \) Hz, CH=CHCOO'Bu), 7.66 (d, 1H, \( J=8.5 \) Hz, Ar-H), 6.38 (d, 1H, \( J=15.8 \) Hz, CH=CHCOO'Bu), 4.67 (s, 2H, Ar-CH₂OCH₂), 3.82 (t, 2H, \( J=6.3 \) Hz, OCH₂CH₂COO'Bu), 2.57 (t, 2H, \( J=6.3 \) Hz, OCH₂CH₂COO'Bu), 1.53 [s, 9H, OC(\( CH_3 \))₃], 1.44 [s, 9H, OC(\( CH_3 \))₃] ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** \( \delta=170.5 \) (s, O=O-C-O), 165.1 (s, O=O-C-O), 148.2 (s, Ar-C), 139.3 (s, Ar-C), 138.8 (s, Ar-C), 137.8 (d, CH=CHCOO'Bu), 127.5 (d, Ar-CH), 125.9 (d, Ar-CH), 123.4 (d, CH=CHCOO'Bu), 122.8 (d, Ar-CH), 81.3 [s, OC(\( CH_3 \))₃], 80.8 [s, OC(\( CH_3 \))₃], 69.7 (t, Ar-CH₂OCH₂), 66.8 (t, OCH₂CH₂COO'Bu), 36.1 (t, OCH₂CH₂COO'Bu), 28.1 [q, 3C, OC(\( CH_3 \))₃], 28.0 [q, 3C, OC(\( CH_3 \))₃] ppm.

**HR-MS (APCI⁺):** m/z calculated for [C₂₇H₂₉NNaO₇]⁺=[M+Na]⁺: 430.1836; found 430.1827.
**Tert-butyl (2E)-3-{2-[(3-tert-butoxy-3-oxopropoxy)methyl]-6-nitrophenyl}acrylate (23s):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21j (100 mg, 0.43 mmol), tertiarybutyl acrylate (276 mg, 2.15 mmol) and Cs₂CO₃ (281 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (9.6 mg, 10 mol%) and PPh₃ (22.6 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 75:25) furnished the diester 23s (132.1 mg, 75%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), Rₖ(21j)=0.25, Rₖ(23s)=0.62, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νₘₐₓ=2978, 1712, 1645, 1529, 1366, 1317, 1148, 1110, 976, 844, 745 cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** δ=7.85 (d, 1H, J=7.9 Hz, Ar-H), 7.76 (d, 1H, J=16.2 Hz, CH=CHCOO'Bu), 7.75 (d, 1H, J=7.9 Hz, Ar-H), 7.45 (t, 1H, J=7.9 Hz, Ar-H), 5.90 (d, 1H, J=16.2 Hz, CH=CHCOO'Bu), 4.50 (s, 2H, Ar-CH₂OCH₂), 3.74 (t, 2H, J=6.4 Hz, OCH₂CH₂COO'Bu), 2.53 (t, 2H, J=6.4 Hz, OCH₂CH₂COO'Bu), 1.51 [s, 9H, OC(CH₃)₃], 1.43 [s, 9H, OC(CH₃)₃] ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** δ=170.6 (s, O=C=O), 164.6 (s, O=C=O), 148.8 (s, Ar-C), 138.8 (s, Ar-C), 137.3 (d, CH=CHCOO'Bu), 132.8 (d, Ar-CH), 129.9 (s, Ar-C), 128.7 (d, Ar-CH), 127.0 (d, CH=CHCOO'Bu), 123.4 (d, Ar-CH), 81.2 [s, OC(CH₃)₃], 80.7 [s, OC(CH₃)₃], 70.0 (t, Ar-CH₂OCH₂), 66.6 (t, OCH₂CH₂COO'Bu), 36.1 (t, OCH₂CH₂COO'Bu), 28.1 [q, 3C, OC(CH₃)₃], 28.0 [q, 3C, OC(CH₃)₃] ppm.

**HR-MS (APCI⁺):** m/z calculated for [C₂₁H₂₉NNaO₇]⁺=[M+Na]⁺: 430.1836; found 430.1851.
**Tert-butyl (2E)-3-[2-[1-(3-tert-butoxy-3-oxopropoxy)ethyl]-4-methoxyphenyl]acrylate (23t):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21I (100 mg, 0.43 mmol), tertiarybutyl acrylate (277 mg, 2.16 mmol) and Cs$_2$CO$_3$ (282 mg, 0.87 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)$_2$ (9.7 mg, 10 mol%) and PPh$_3$ (22.7 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 80:20) furnished the diester 23t (129.8 mg, 74%) as a pale pink viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), $R_f$ (21I) = 0.45, $R_f$ (23t) = 0.66, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{\text{max}}$ = 2976, 2932, 1729, 1704, 1629, 1602, 1492, 1366, 1291, 1250, 1143, 1104, 979, 849 cm$^{-1}$.

**$^1$H-NMR (CDCl$_3$, 400 MHz):** $\delta$ = 7.86 (d, 1H, $J$=15.7 Hz, CH=CHCOO$t$Bu), 7.49 (d, 1H, $J$=8.7 Hz, Ar-H), 7.03 (d, 1H, $J$=2.8 Hz, Ar-H), 6.78 (dd, 1H, $J$=8.7 and 2.8 Hz, Ar-H), 6.17 (d, 1H, $J$=15.7 Hz, CH=CHCOO$t$Bu), 4.79 (q, 1H, $J$=6.5 Hz, Ar-CHCH$_3$), 3.83 (s, 3H, Ar-OCH$_3$), 3.56 (ddd, 1H, $J$=12.9, 9.3 and 6.5 Hz, OCH$_2$CH$_2$COO$t$Bu), 3.53 (ddd, 1H, $J$=12.9, 9.3 and 6.5 Hz, OCH$_2$CH$_2$COO$t$Bu), 2.48 (t, 2H, $J$=6.5 Hz, OCH$_2$CH$_2$COO$t$Bu), 1.52 [s, 9H, OC(CH$_3$)$_3$], 1.43 [s, 9H, OC(CH$_3$)$_3$], 1.37 (d, 3H, $J$=6.5 Hz, Ar-CH$CH_3$) ppm.

**$^{13}$C-NMR (CDCl$_3$, 100 MHz):** $\delta$ = 170.8 (s, O=C–O), 166.5 (s, O=C–O), 161.4 (s, Ar-C), 145.1 (s, Ar-C), 139.6 (d, CH=CHCOO$t$Bu), 128.1 (d, Ar-CH), 124.7 (s, Ar-C), 119.5 (d, CH=CHCOO$t$Bu), 113.6 (d, Ar-CH), 110.6 (d, Ar-CH), 80.5 [s, OC(CH$_3$)$_3$], 80.3 [s, OC(CH$_3$)$_3$], 74.5 (d, Ar-CH$CH_3$), 64.7 (t, OCH$_2$CH$_2$COO$t$Bu), 55.3 (q, Ar-OCH$_3$), 36.4 (t, OCH$_2$CH$_2$COO$t$Bu), 28.2 [q, 3C, OC(CH$_3$)$_3$], 28.1 [q, 3C, OC(CH$_3$)$_3$], 23.9 (q, Ar-CH$CH_3$) ppm.

**HR-MS (APCI$^+$):** m/z calculated for [C$_{23}$H$_{34}$NaO$_6$]$^+$=[M+Na]$^+$: 429.2248; found 429.2256.
**Tert-Butyl (2E)-3-[6-[1-(3-tert-butoxy-3-oxopropanoyl)ethyl]-1,3-benzodioxol-5-yl]acrylate (23u):**

GP-2 was carried out with the 2-bromobenzyl alcohol 21m (100 mg, 0.41 mmol), tertiarybutyl acrylate (261.2 mg, 2.04 mmol) and Cs₂CO₃ (266 mg, 0.82 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture, were added Pd(OAc)₂ (9.1 mg, 10 mol%) and PPh₃ (21.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (Petroleum ether/ethyl acetate, 98:2 to 85:15) furnished the diester 23u (145.9 mg, 85%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), Rf(1l)=0.47, Rf(3dl)=0.65, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** \( \nu_{\text{max}} = 2976, 1730, 1707, 1628, 1617, 1482, 1367, 1288, 1253, 1153, 1104, 1040, 849 \text{ cm}^{-1} \).

**1H-NMR (CDCl₃, 400 MHz):** \( \delta = 7.83 \text{ (d, 1H, } J=15.6 \text{ Hz, CH=CHCOO}^\text{tBu}), 6.98 \text{ (s, 1H, Ar-H)}, 6.96 \text{ (s, 1H, Ar-H)}, 6.13 \text{ (d, 1H, } J=15.6 \text{ Hz, CH=CHCOO}^\text{tBu}), 5.97 \text{ (d, 1H, } J=1.2 \text{ Hz, O-CH₂A-O}), 5.95 \text{ (d, 1H, } J=1.2 \text{ Hz, O-CH₂B-O}), 4.77 \text{ (q, 1H, } J=6.4 \text{ Hz, Ar-CHCH₃}), 3.53 \text{ (ddd, 1H, } J=12.0, 9.3 \text{ and } 6.5 \text{ Hz, OCH₂CH₂COO}^\text{tBu}), 3.50 \text{ (ddd, 1H, } J=12.0, 9.3 \text{ and } 6.5 \text{ Hz, OCH₂CH₂COO}^\text{tBu}), 2.46 \text{ (t, 2H, } J=6.5 \text{ Hz, OCH₂CH₂COO}^\text{tBu}), 1.52 \text{ [s, 9H, OC(CH₃)₃]}, 1.44 \text{ [s, 9H, OC(CH₃)₃]}, 1.33 \text{ (d, 3H, } J=6.4 \text{ Hz, Ar-CHCH₃}) \text{ ppm.}

**13C-NMR (CDCl₃, 100 MHz):** \( \delta = 170.8 \text{ (s, O=C–O)}, 166.4 \text{ (s, O=C–O)}, 149.7 \text{ (s, Ar-C)}, 147.1 \text{ (s, Ar-C)}, 139.4 \text{ (d, CH=CHCOO}^\text{tBu}), 138.8 \text{ (s, Ar-C)}, 125.9 \text{ (s, Ar-C)}, 120.0 \text{ (d, Ar-CH)}, 120.1 \text{ (d, CH=CHCOO}^\text{tBu}), 106.0 \text{ (d, Ar-CH)}, 105.6 \text{ (d, Ar-CH)}, 101.4 \text{ (t, O-CH₂-O)}, 80.5 \text{ [s, OC(CH₃)₃]}, 80.4 \text{ [s, OC(CH₃)₃]}, 74.0 \text{ (d, Ar-CHCH₃)}, 64.6 \text{ (t, OCH₂CH₂COO}^\text{tBu}), 36.5 \text{ (t, OCH₂CH₂COO}^\text{tBu}), 28.2 \text{ [q, 3C, OC(CH₃)₃]}, 28.1 \text{ [q, 3C, OC(CH₃)₃]}, 24.0 \text{ (d, Ar-CHCH₃)} \text{ ppm.}
HR-MS (APCI⁺): m/z calculated for [C_{23}H_{32}NaO_7]^+=[M+Na]^+: 443.2040; found 443.2042.

**Tert-Butyl** (2E)-3-[2-[1-(3-tert-butoxy-3-oxopropoxy)ethyl]-4,5-dimethoxyphenyl]acrylate (23v):

GP-2 was carried out with the 2-bromobenzyl alcohol 21o (100 mg, 0.38 mmol), tertiarybutyl acrylate (245 mg, 1.91 mmol) and Cs_2CO_3 (250 mg, 0.76 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (8.6 mg, 10 mol%) and PPh₃ (20.1 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester 23v (112.3 mg, 67%) as a colorless semi-solid. [TLC control (petroleum ether/ethyl acetate 70:30), R_f (21o)=0.45, R_f (23v)=0.60, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** ν_max=2976, 2932, 1729, 1705, 1601, 1511, 1367, 1287, 1267, 1152, 1105, 847 cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** δ=7.88 (d, 1H, J=15.7 Hz, CH=CHCOO'Bu), 7.02 (s, 1H, Ar-H), 7.00 (s, 1H, Ar-H), 6.18 (d, 1H, J=15.7 Hz, CH=CHCOO'Bu), 4.81 [q, 1H, J=6.4 Hz, Ar-CH(CH₃)OCH₂], 3.92 (s, 3H, Ar-OCH₃), 3.88 (s, 3H, Ar-OCH₃), 3.55 (ddd, 1H, J=13.3, 9.3 and 6.8 Hz, OCH₂CH₂COO'Bu), 3.55 (ddd, 1H, J=13.3, 9.3 and 6.8 Hz, OCH₂CH₂COO'Bu), 2.47 (t, 2H, J=6.8 Hz, OCH₂CH₂COO'Bu), 1.53 [s, 9H, OC(CH₃)₃], 1.43 [s, 9H, OC(CH₃)₃], 1.37 [d, 3H, J=6.4 Hz, Ar-CH(CH₃)OCH₂] ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** δ=170.8 (s, O=O-C=O), 166.5 (s, O=O-C=O), 151.2 (s, Ar-C), 148.1 (s, Ar-C), 139.5 (d, CH=CHCOO'Bu), 137.0 (s, Ar-C), 124.4 (s, Ar-C), 119.5 (d, CH=CHCOO'Bu), 108.5 (d, Ar-CH), 108.4 (d, Ar-CH), 80.5 [s, 2C, 2 × OC(CH₃)₃], 74.0 [d, Ar-CH(CH₃)OCH₂], 64.5 (t, OCH₂CH₂COO'Bu), 56.0
(q, Ar-OCH₃), 55.9 (q, Ar-OCH₃), 36.4 (t, OCH₂CH₂COO'Bu), 28.2 [q, 3C, OC(CH₃)₃], 28.1 [q, 3C, OC(CH₃)₃], 24.2 [q, Ar-CH(CH₃)OCH₂] ppm.

HR-MS (ESI⁺): m/z calculated for [C_{24}H_{36}NaO₇]^⁺=[M+Na]^⁺: 459.2353; found 459.2324.

Methyl (2E)-3-[4-(benzyloxy)-5-methoxy-2-[(3-methoxy-3-oxopropoxy)methyl]phenyl]acrylate (23w):

GP-2 was carried out with the 2-bromobenzyl alcohol 21d (100 mg, 0.31 mmol), methyl acrylate (134 mg, 1.55 mmol) and Cs₂CO₃ (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (6.8 mg, 10 mol%) and PPh₃ (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the diester 23w (34 mg, 26%) as a pale yellow viscous liquid. [TLC control (benzene/ethyl acetate 80:20), R_f(21d)=0.50, R_f(23w)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): ν_max=2951, 2927, 2870, 1737, 1716, 1631, 1601, 1514, 1454, 1384, 1276, 1170, 1111, 1026, 859, 739, 699 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.89 (d, 1H, J=15.8 Hz, CH=CHCOOMe), 7.43 (d, 2H, J=7.2 Hz, Ar-H), 7.36 (dd, 2H, J=7.2 and 7.2 Hz, Ar-H), 7.29 (t, 1H, J=7.2 Hz, Ar-H), 7.09 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.27 (d, 1H, J=15.8 Hz, CH=CHCOOMe), 5.18 (s, 2H, PhCH₂OAr), 4.55 (s, 2H, ArCH₂OCH₂), 3.89 (s, 3H, Ar-OCH₃), 3.79 (s, 3H, O=C-OCH₃), 3.69 (t, 2H, 6.4 Hz, OCH₂CH₂COOMe), 3.67 (s, 3H, O=C-OCH₃), 2.57 (t, 2H, J=6.4 Hz, OCH₂CH₂COOMe) ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=171.9 (s, O=C–O), 167.5 (s, O=C–O), 149.8 (s, Ar-C), 149.2 (s, Ar-C), 141.2 (d, CH=CHCOOMe), 136.5 (s, Ar-C), 130.7 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.3 (d, 2C, Ar-CH), 126.0 (s, Ar-C), 117.3 (d, Ar-CH), 114.3 (d, Ar-CH), 109.5 (d, CH=CHCOOMe), 70.8 (t,
PhCH$_2$OAr), 70.2 (t, Ar-CH$_2$OCH$_2$), 65.6 (t, OCH$_2$CH$_2$COOMe), 56.1 (q, Ar-OCH$_3$), 51.7 (q, O=C-OCH$_3$), 51.6 (q, O=C-OCH$_3$), 34.8 (t, OCH$_2$CH$_2$COOMe) ppm.

**HR-MS (ESI$^+$):** m/z calculated for [C$_{23}$H$_{25}$O$_6$]$^+=$(M+H)−H$_2$O$^+$: 397.1645; found 397.1664.

![Diagram of molecular structure](image.png)

Methyl (2E)-3-(4,5-dimethoxy-2-[(3-methoxy-3-oxoproxy)methyl]phenyl)acrylate (23x):

GP-2 was carried out with the 2-bromobenzyl alcohol 21g (100 mg, 0.40 mmol), methyl acrylate (174 mg, 2.02 mmol) and Cs$_2$CO$_3$ (264 mg, 0.81 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)$_2$ (9.1 mg, 10 mol%) and PPh$_3$ (21.2 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 70:30) furnished the diester 23x (44 mg, 32%) as a yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 30:20), $R_f$(21g)=0.40, $R_f$(23x)=0.35, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{max}$=2951, 2868, 1736, 1714, 1631, 1601, 1516, 1438, 1271, 1170, 1111, 1029, 860 cm$^{-1}$.

**$^1$H-NMR (CDCl$_3$, 400 MHz):** $\delta$=7.91 (d, 1H, $J$=15.8 Hz, CH=CHCOOMe), 7.07 (s, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 6.27 (d, 1H, $J$=15.8 Hz, CH=CHCOOMe), 4.60 (s, 2H, Ar-CH$_2$OCH$_2$), 3.91 (s, 3H, Ar-OCH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 3.80 (s, 3H, O=O-OCH$_3$), 3.78 (t, 2H, $J$=6.4 Hz, OCH$_2$CH$_2$COOMe), 3.68 (s, 3H, O=O-OCH$_3$), 2.63 (t, 2H, $J$=6.4 Hz, OCH$_2$CH$_2$COOMe) ppm.

**$^{13}$C-NMR (CDCl$_3$, 100 MHz):** $\delta$=171.9 (s, O=O-C-O), 167.5 (s, O=O-C-O), 150.7 (s, Ar-C), 148.7 (s, Ar-C), 141.2 (d, CH=CHCOOMe), 130.9 (s, Ar-C), 125.7 (s, Ar-C), 117.3 (d, CH=CHCOOMe), 112.2 (d, Ar-CH), 109.0 (d, Ar-CH), 70.3 (t,
Ar-CH₂OCH₂), 65.8 (t, OCH₂CH₂COOCH₃), 56.0 (q, 2C, 2 × Ar-OCH₃), 51.7 (q, O=C-OCH₃), 51.6 (q, O=C-OCH₃), 34.9 (t, OCH₂CH₂COOMe) ppm.

HR-MS (ESI⁺): m/z calculated for [C₁₇H₂₂NaO₇]⁺=[M+Na]⁺: 361.1258; found 361.1271.

(2E)-3-{6-[(2-Cyanoethoxy)methyl]-1,3-benzodioxol-5-yl}acrylonitrile (23y):

GP-2 was carried out with the 2-bromobenzyl alcohol 21f (100 mg, 0.43 mmol), acrylonitrile (115 mg, 2.16 mmol) and Cs₂CO₃ (282 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (9.7 mg, 10 mol%) and PPh₃ (23 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 85:15 to 65:35) furnished the diester 23y (28.2 mg, 25%) as a yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 60:40), Rf(21f)=0.55, Rf(23y)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νmax=2907, 2215, 1600, 1504, 1484, 1273, 1254, 1100, 1038, 930 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.62 (d, 1H, J=16.4 Hz, CH=CHCN), 6.97 (s, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 6.02 (s, 2H, O-CH₂-O), 5.68 (d, 1H, J=16.4 Hz, CH=CHCN), 4.55 (s, 2H, Ar-CH₂OCH₂), 3.68 (t, 2H, J=6.4 Hz, OCH₂CH₂CN), 2.62 (t, 2H, J=6.4 Hz, OCH₂CH₂CN) ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=150.1 (s, Ar-C), 148.4 (s, Ar-C), 146.7 (d, CH=CHCN), 131.2 (s, Ar-C), 126.9 (s, Ar-C), 118.3 (s, CH₂CH₂CN), 117.4 (s, CH=CHCN), 110.1 (d, Ar-CH), 105.3 (d, Ar-CH), 102.0 (t, O-CH₂-O), 96.1 (d, CH=CHCN), 70.7 (t, Ar-CH₂OCH₂), 64.8 (t, OCH₂CH₂CN), 18.9 (t, OCH₂CH₂CN) ppm.

HR-MS (ESI⁺): m/z calculated for [C₁₄H₁₂N₂O₃]⁺=[M]⁺: 256.0842; found 256.0849.
7-(Benzyloxy)-4-methyl-1H-isochromene (28a'):

GP-3 was carried out with the 2-bromobenzyl alcohol 21b (100 mg, 0.34 mmol), allyl bromide (82.6 mg, 0.68 mmol) and NaH (32.8 mg, 1.36 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added Pd(OAc)$_2$ (7.6 mg, 10 mol%), PPh$_3$ (18.0 mg, 20 mol%) and triethylbenzylammonium chloride (78 mg, 0.34 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1 to 98:2) furnished the isochromene 28a' (24.1 mg, 28%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), $R_f(21b)=0.15$, $R_f(28a')=0.74$, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=2963, 2859, 1639, 1608, 1498, 1454, 1381, 1301, 1281, 1246, 1168, 1129, 1081, 1022, 926, 839, 807, 734, 695 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta=7.46$–7.26 (m, 5H, Ar-H), 7.03 (d, 1H, $J=8.3$ Hz, Ar-H), 6.88 (dd, 1H, $J=8.3$ and 2.4 Hz, Ar-H), 6.68 (d, 1H, $J=2.4$ Hz, Ar-H), 6.39 [d, 1H, $J=1.5$ Hz, ArC(Me)=CHOCH$_3$], 5.06 (s, 2H, PhCH$_2$O), 4.95 (s, 2H, ArCH$_2$O), 1.89 (d, 3H, $J=1.5$ Hz, CH=C(CH$_3$)$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta=157.8$ (s, Ar-C), 140.4 (d, CH=CCH$_3$), 136.9 (s, Ar-C), 130.5 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 125.6 (s, CH=C(CH$_3$)$_3$), 121.6 (d, Ar-CH), 113.6 (d, Ar-CH), 111.2 (s, Ar-C), 111.1 (d, Ar-CH), 70.1 (t, PhCH$_2$O), 68.2 (t, ArCH$_2$O), 13.1 (q, CH=CCH$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{17}$H$_{17}$O$_2$]$^+=[M+H]$^+$: 253.1223; found 253.1225.
7-(Benzyloxy)-4-methylene-3,4-dihydro-1H-isochromene (28a):

Further elution of the column (petroleum ether/ethyl acetate, 98:2 to 95:5) yielded the isochromene 28a (53.3 mg, 62%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), Rf(21b)=0.15, Rf(28a)=0.65, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νmax=2954, 2825, 1634, 1606, 1571, 1496, 1453, 1310, 1276, 1231, 1168, 1110, 1085, 1023, 880, 737, 696 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.61 (d, 1H, J=8.8 Hz, Ar-H), 7.46–7.27 (m, 5H, Ar-H), 6.87 (dd, 1H, J=8.8 and 2.6 Hz, Ar-H), 6.61 (d, 1H, J=2.6 Hz, Ar-H), 5.46 (s, 1H, ArC=CH₂A), 5.06 (s, 2H, PhCH₂O), 4.89 (s, 1H, ArC=CH₂B), 4.76 (s, 2H, ArCH₂OCH₂), 4.42 (s, 2H, ArCH₂OCH₂) ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=158.6 (s, Ar-C), 137.9 (s, Ar-C), 136.7 (s, Ar-C), 136.0 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 125.0 (d, Ar-CH), 124.2 (s, ArC=CH₂), 114.4 (d, Ar-CH), 109.9 (d, Ar-CH), 104.7 (t, ArC=CH₂), 71.1 (t, PhCH₂O), 70.3 (t, ArCH₂OCH₂), 69.1 (t, ArCH₂OCH₂) ppm.

HR-MS (APCI⁺): m/z calculated for [C₁₇H₁₇O₂⁺]=[M+H]⁺: 253.1223; found 253.1224.

7-(Methoxy)-4-methyl-1H-isochromene (28b) :

GP-3 was carried out with the 2-bromobenzyl alcohol 21c (100 mg, 0.46 mmol), allyl bromide (111.5 mg, 0.92 mmol) and NaH (44.2 mg, 1.84 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added Pd(OAc)₂ (10.3 mg, 10 mol%), PPh₃ (24.2
160 mg, 20 mol%) and triethylbenzylammonium chloride (105 mg, 0.46 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1 to 98:2) furnished the isochromene 28b’ (21.2 mg, 26%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), Rf(21c)=0.14, Rf(28b’)=0.70, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νmax=2961, 2935, 2834, 1639, 1610, 1573, 1501, 1464, 1431, 1307, 1282, 1250, 1163, 1130, 1074, 1034, 946, 917, 838, 811, 781 cm⁻¹.

**1H-NMR (CDCl₃, 400 MHz):** δ=7.02 (d, 1H, J=8.8 Hz, Ar-H), 6.80 (dd, 1H, J=8.8 and 2.9 Hz, Ar-H), 6.59 (d, 1H, J=2.9 Hz, Ar-H), 6.38 [q, 1H, J=1.5 Hz, ArC(Me)=CHOCH₂], 4.95 (s, 2H, ArCH₂O), 3.79 (s, 3H, Ar-OCH₃), 1.89 (d, 3H, J=1.5 Hz, CH=CC₂H₃) ppm.

**13C-NMR (CDCl₃, 100 MHz):** δ=158.7 (s, Ar-C), 140.3 (d, CH=CCH₃), 130.5 (s, Ar-C), 125.4 (s, Ar-C), 121.6 (d, Ar-CH), 112.6 (d, Ar-CH), 111.2 (s, CH=CCH₃), 110.1 (d, Ar-CH), 68.2 (t, ArCH₂O), 55.3 (q, Ar-OCH₃), 13.1 (q, CH=CCH₃) ppm.

**HR-MS (APCI⁺):** m/z calculated for [C₁₁H₁₃O₂]⁺=[M+H]⁺: 177.0910; found 177.0905.

Further elution of the column (petroleum ether/ethyl acetate, 98:2 to 93:7) yielded the isochromene 28b (49.3 mg, 61%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), Rf(21c)=0.14, Rf(28b)=0.60, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νmax=2955, 2833, 1632, 1605, 1497, 1452, 1310, 1278, 1269, 1234, 1110, 1086, 1031, 961, 881, 819, 768 cm⁻¹.
^1^H-NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta=7.61\) (d, 1H, \(J=8.8\) Hz, Ar-H), 6.80 (dd, 1H, \(J=8.8\) and 2.9 Hz, Ar-H), 6.53 (d, 1H, \(J=2.9\) Hz, Ar-H), 5.46 (s, 1H, ArC=CH\textsubscript{2}A), 4.89 (s, 1H, ArC=CH\textsubscript{2}B), 4.77 (s, 2H, ArCH\textsubscript{2}OCH\textsubscript{2}), 4.41 (s, 2H, ArCH\textsubscript{2}OCH\textsubscript{2}), 3.80 (s, 3H, Ar-OC\textsubscript{H}\textsubscript{3}) ppm.

^13^C-NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta=159.4\) (s, Ar-C), 137.9 (s, Ar-C), 136.0 (s, Ar-C), 125.0 (d, Ar-CH), 123.9 (s, ArC=CH\textsubscript{2}), 113.6 (d, Ar-CH), 108.7 (d, Ar-CH), 104.6 (t, ArC=CH\textsubscript{2}), 71.1 (t, ArCH\textsubscript{2}OCH\textsubscript{2}), 69.1 (t, ArCH\textsubscript{2}OCH\textsubscript{2}), 55.3 (q, Ar-OC\textsubscript{H}\textsubscript{3}) ppm.

HR-MS (APCI\textsuperscript{+}): m/z calculated for \([C_{11}H_{13}O_{2}]^+=[M+H]^+\): 177.0910; found 177.0903.

\[\text{8-Methyl-5H-[1,3]dioxolo[4,5-g]isochromene (28c')}:\]

GP-3 was carried out with the 2-bromobenzyl alcohol 21f (100 mg, 0.43 mmol), allyl bromide (104.8 mg, 0.86 mmol) and NaH (42 mg, 1.73 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added Pd(OAc)\textsubscript{2} (9.7 mg, 10 mol%), PPh\textsubscript{3} (22.7 mg, 20 mol%) and triethylbenzylammonium chloride (99 mg, 0.43 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1 to 98:2) furnished the isochromene 28c' (10.2 mg, 12%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), \(R_f(21f)=0.15, R_f(28c')=0.71\), UV detection].

IR (neat; MIR-ATR, 4000–600 cm\textsuperscript{-1}): \(\nu_{\text{max}}=2962, 2892, 1644, 1502, 1482, 1444, 1379, 1272, 1239, 1172, 1138, 1108, 1037, 1026, 980, 933, 856, 840, 790\) cm\textsuperscript{-1}.
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta=6.64$ (s, 1H, Ar-H), 6.55 (s, 1H, Ar-H), 6.40 [q, 1H, $J=1.5$ Hz, ArC(Me)=CHOCH$_2$], 5.92 (s, 2H, OCH$_2$O), 4.87 (s, 2H, ArCH$_2$O), 1.88 (d, 3H, $J=1.5$ Hz, CH=CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta=147.4$ (s, Ar-C), 145.9 (s, Ar-C), 140.9 (d, CH=CH$_3$), 127.0 (s, Ar-C), 122.2 (s, Ar-C), 111.5 (s, CH=CH$_3$), 105.1 (d, Ar-CH), 101.9 (d, Ar-CH), 100.9 (t, OCH$_2$O), 68.2 (t, ArCH$_2$O), 13.4 (q, CH=CH$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{11}$H$_{11}$O$_3$]$^+=[M+H]$^+$: 191.0703; found 191.0694.

8-Methylene-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochromene (28c):

Further elution of the column (petroleum ether/ethyl acetate, 98:2 to 94:6) yielded the isochromene 28c (64.3 mg, 78%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), $R_s$(21f)=0.15, $R_s$(28c)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=2893, 2827, 1622, 1502, 1479, 1442, 1357, 1341, 1289, 1238, 1217, 1176, 1099, 1035, 936, 921, 879, 859, 835, 779 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta=7.10$ (s, 1H, Ar-H), 6.46 (s, 1H, Ar-H), 5.93 (s, 2H, OCH$_2$O), 5.38 (s, 1H, ArC=CH$_2$A), 4.88 (s, 1H, ArC=CH$_2$B), 4.69 (s, 2H, ArCH$_2$OCH$_2$), 4.38 (s, 2H, ArCH$_2$OCH$_2$) ppm.

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta=147.7$ (s, Ar-C), 147.0 (s, Ar-C), 138.1 (s, Ar-C), 128.8 (s, Ar-C), 124.9 (s, ArC=CH$_2$), 105.1 (t, ArC=CH$_2$), 104.4 (d, Ar-CH), 103.2 (d, Ar-CH), 101.0 (t, OCH$_2$O), 70.7 (t, ArCH$_2$OCH$_2$), 68.9 (t, ArCH$_2$OCH$_2$) ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{11}$H$_{11}$O$_3$]$^+=[M+H]$^+$: 191.0703; found 191.0697.
6,7-Dimethoxy-4-methyl-1H-isochromene (28d):

GP-3 was carried out with the 2-bromobenzyl alcohol 21g (100 mg, 0.40 mmol) with allyl bromide (98 mg, 0.81 mmol) and NaH (39 mg, 1.62 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added Pd(OAc)$_2$ (9.1 mg, 10 mol%), PPh$_3$ (21.3 mg, 20 mol%) and triethylbenzylammonium chloride (92.2 mg, 0.40 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to 94:6) furnished the isochromene 28d' (20.0 mg, 24%) as a pale yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 85:15), $R_f(21g)=0.15$, $R_f(28d')=0.70$, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{max}=2963, 2936, 2834, 1637, 1604, 1508, 1460, 1449, 1379, 1351, 1261, 1244, 1155, 1130, 1061, 1004, 860, 764$ cm$^{-1}$.

**$^1$H-NMR (CDCl$_3$, 400 MHz):** $\delta=6.58$ (s, 1H, Ar-H), 6.51 (s, 1H, Ar-H), 6.33 [q, 1H, $J=1.3$ Hz, ArC(Me)=CHOCH$_2$], 4.85 (s, 2H, ArCH$_2$O), 3.82 (s, 3H, Ar-OCH$_3$), 3.79 (s, 3H, Ar-OCH$_3$), 1.83 (d, 3H, $J=1.3$ Hz, CH=CCH$_3$) ppm.

**$^{13}$C-NMR (CDCl$_3$, 100 MHz):** $\delta=148.8$ (s, Ar-C), 147.8 (s, Ar-C), 140.7 (d, CH=CCH$_3$), 125.6 (s, CH=CCH$_3$), 121.0 (s, Ar-C), 111.1 (s, Ar-C), 108.0 (d, Ar-CH), 104.9 (d, Ar-CH), 67.9 (t, ArCH$_2$O), 56.1 (2 × q, 2C, 2 × Ar-OCH$_3$), 13.2 (q, CH=CCH$_3$) ppm.

**HR-MS (APCI$^+$):** m/z calculated for [C$_{12}$H$_{15}$O$_3$]$^+=[M+H]$^+$: 207.1016; found 207.1015.

6,7-Dimethoxy-4-methylene-3,4-dihydro-1H-isochromene(28d):
Further elution of the column (petroleum ether/ethyl acetate, 94:6 to 90:10) yielded the isochromene 28d (50.9 mg, 61%) as a white semi-solid. [TLC control (petroleum ether/ethyl acetate 85:15), \( R_f(21g) = 0.15 \), \( R_f(28d) = 0.62 \), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \( \nu_{\text{max}} = 2960, 2826, 1604, 1509, 1461, 1342, 1289, 1265, 1244, 1161, 1070, 1034, 991, 940, 881, 857, 768 \text{ cm}^{-1} \).

**\(^1\)H-NMR (CDCl\(_3\), 400 MHz)**: \( \delta = 7.12 \) (s, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 5.42 (s, 1H, ArC=CH\(_2\)), 4.90 (s, 1H, ArC=CH\(_2\)), 4.73 (s, 2H, ArCH\(_2\)OCH\(_2\)), 4.40 (s, 2H, ArCH\(_2\)OCH\(_2\)), 3.89 (s, 3H, Ar-\text{OCH}_3), 3.85 (s, 3H, Ar-\text{OCH}_3) ppm.

**\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz)**: \( \delta = 149.6 \) (s, Ar-C), 148.2 (s, Ar-C), 138.1 (s, Ar-C), 127.6 (s, Ar-C), 123.5 (s, ArC=CH\(_2\)), 106.9 (d, Ar-CH), 106.0 (d, Ar-CH), 104.6 (t, ArC=CH\(_2\)), 70.8 (t, ArCH\(_2\)OCH\(_2\)), 68.7 (t, ArCH\(_2\)OCH\(_2\)), 56.0 (q, Ar-OCH\(_3\)), 55.9 (q, Ar-OCH\(_3\)) ppm.

**HR-MS (APCI\(^+\))**: \( m/z \) calculated for \([\text{C}_{12}\text{H}_{15}\text{O}_3]^+ = [\text{M+H}]^+ \): 207.1016; found 207.1013.

![Image of isochromene 28e'](#image)

**5,6,7-Trimethoxy-4-methyl-1H-isochromene (28e')**: GP-3 was carried out with the 2-bromobenzyl alcohol 21h (100 mg, 0.36 mmol), allyl bromide (87.4 mg, 0.72 mmol) and NaH (34.7 mg, 1.44 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added Pd(OAc)\(_2\) (8.1 mg, 10 mol%), PPh\(_3\) (18.9 mg, 20 mol%) and triethylbenzylationmonium chloride (82.2 mg, 0.36 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to 95:5) furnished the isochromene 28e' (10.9 mg, 13%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), \( R_f(21h) = 0.15 \), \( R_f(28e') = 0.65 \), UV detection].
IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 2936, 2836, 1628, 1598, 1486, 1455, 1406, 1377, 1232, 1195, 1134, 1105, 1016, 951, 830 \) cm⁻¹.

\(^1\)H-NMR (CDCl₃, 400 MHz): \( \delta = 6.40 \) (s, 1H, Ar-H), 6.35 [q, 1H, \( J = 1.4 \) Hz, ArC(Me)=CHOCH₂], 4.78 (s, 2H, ArCH₂O), 3.84 (s, 3H, Ar-OCH₃), 3.83 (s, 3H, Ar-OCH₃), 3.81 (s, 3H, Ar-OCH₃), 2.06 (d, 3H, \( J = 1.4 \) Hz, CH=CC₃H₃) ppm.

\(^13\)C-NMR (CDCl₃, 100 MHz): \( \delta = 152.0 \) (s, Ar-C), 149.8 (s, Ar-C), 142.6 (s, Ar-C), 141.5 (d, CH=CCH₃), 126.0 (s, Ar-C), 118.8 (s, CH=CCH₃), 111.9 (s, Ar-C), 104.2 (d, Ar-CH), 68.6 (t, ArCH₂O), 61.1 (q, Ar-OCH₃), 60.8 (q, Ar-OCH₃), 56.1 (q, Ar-OCH₃), 16.1 (q, CH=CCH₃) ppm.

HR-MS (APCI⁺): m/z calculated for \([\text{C}_{13}\text{H}_{16}\text{NaO}_4]^+ = [\text{M}+\text{Na}]^+\): 259.0941; found 259.0929.

5,6,7-Trimethoxy-4-methylene-3,4-dihydro-1H-isochromene (28e):

Further elution of the column (petroleum ether/ethyl acetate, 95:5 to 90:10) yielded cyclic ether 28e (59.6 mg, 70%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), \( R_f(21h) = 0.15, R_f(28e) = 0.50, \text{UV detection} \].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 2937, 2834, 1630, 1595, 1489, 1454, 1333, 1289, 1235, 1107, 1039, 1022, 930 \) cm⁻¹.

\(^1\)H-NMR (CDCl₃, 400 MHz): \( \delta = 6.32 \) (s, 1H, Ar-H), 6.06 (s, 1H, ArC=CH₂A), 5.12 (s, 1H, ArC=CH₂B), 4.73 (s, 2H, ArCH₂OCH₂), 4.32 (s, 2H, ArCH₂OCH₂), 3.85 (s, 3H, Ar-OCH₃), 3.84 (s, 3H, Ar-OCH₃), 3.83 (s, 3H, Ar-OCH₃) ppm.

\(^13\)C-NMR (CDCl₃, 100 MHz): \( \delta = 153.0 \) (s, 2C, Ar-C), 141.5 (s, Ar-C), 135.1 (s, Ar-C), 131.4 (s, Ar-C), 118.0 (s, ArC=CH₂), 111.5 (t, ArC=CH₂), 103.1 (d, Ar-CH), 72.7 (t, ArCH₂OCH₂), 69.1 (t, ArCH₂OCH₂), 60.9 (q, Ar-OCH₃), 59.8 (q, Ar-OCH₃), 55.9 (q, Ar-OCH₃) ppm.
**HR-MS (APCI⁺):** m/z calculated for \([C_{13}H_{17}O_{4}]^+=[M+H]^+\): 237.1121; found 237.1125.

![Methoxy-1,4-dimethyl-1H-isochromene (28f')](image)

**7-Methoxy-1,4-dimethyl-1H-isochromene (28f'):**

**GP-3** was carried out with the 2-bromobenzyl alcohol 211 (100 mg, 0.43 mmol), allyl bromide (104.8 mg, 0.87 mmol) and NaH (41.6 mg, 1.73 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added Pd(OAc)₂ (9.7 mg, 10 mol%), PPh₃ (22.7 mg, 20 mol%) and triethylbenzylammonium chloride (98.6 mg, 0.43 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1 to 98:2) furnished the isochromene 28f' (18.0 mg, 22%) as a yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), \(R_f(211)=0.15, R_f(28f')=0.70\), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** \(\nu_{max}=2976, 2924, 2851, 1608, 1571, 1498, 1468, 1374, 1273, 1234, 1170, 1096, 1053, 927, 849, 816\) cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** \(\delta=7.03\) (d, 1H, \(J=8.8\) Hz, Ar-H), 6.78 (dd, 1H, \(J=8.8\) and 2.4 Hz, Ar-H), 6.61 (d, 1H, \(J=2.4\) Hz, Ar-H), 6.31 [q, 1H, \(J=1.5\) Hz, ArC(Me)=CHOCH₂], 5.09 [q, 1H, \(J=6.4\) Hz, ArCH(Me)O], 3.80 (s, 3H, Ar-OCH₃), 1.88 (d, 3H, \(J=1.5\) Hz, CH=CH₃), 1.56 [d, 3H, \(J=6.4\) Hz, ArCHO(CH₃)] ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** \(\delta=158.7\) (s, ArC), 138.9 (d, CH=CH₃), 134.9 (s, ArC), 124.8 (s, ArC), 121.7 (d, ArCH), 111.9 (d, ArCH), 110.2 [s, ArC(CH₃)=COCH₃], 109.9 (d, ArCH), 73.2 [d, ArCH(CH₃)], 55.3 (q, ArOCH₃), 19.6 [q, ArCO(CH₃)], 13.2 (q, CH=CH₃) ppm.

**HR-MS (APCI⁺):** m/z calculated for \([C_{12}H_{15}O_{2}]^+=[M+H]^+\): 191.1067; found 191.1063.
Further elution of the column (petroleum ether/ethyl acetate, 98:2 to 90:10) yielded the isochromene 28f (42 mg, 51%) as a colorless oil. [TLC control (petroleum ether/ethyl acetate 90:10), \( R_f(21i) = 0.15, R_f(28f) = 0.61 \), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \( \nu_{max} = 2957, 2923, 2850, 1607, 1493, 1463, 1302, 1276, 1119, 1089, 1067, 876, 850, 818 \) cm\(^{-1}\).

**\(^1\)H-NMR (CDCl\(_3\), 400 MHz)**: \( \delta = 7.60 \) (d, 1H, \( J=8.8 \) Hz, Ar-H), 6.80 (d, 1H, \( J=8.8 \) and 2.4 Hz, Ar-H), 6.61 (d, 1H, \( J=2.4 \) Hz, Ar-H), 5.44 (s, 1H, ArC=CH\(_2\)A), 4.87 (s, 1H, ArC=CH\(_2\)B), 4.85 [q, 1H, \( J=6.4 \) Hz, ArCH(CH\(_3\))OCH\(_2\)], 4.50 [d, 1H, \( J=13.2 \) Hz, ArCH(Me)OC\(_2\)H\(_2\)A], 4.32 [d, 1H, \( J=13.2 \) Hz, ArCH(Me)OCH\(_2\)B], 3.81 (s, 3H, Ar-OCH\(_3\)), 1.55 [d, 3H, \( J=6.4 \) Hz, ArCH(CH\(_3\))O] ppm.

**\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz)**: \( \delta = 159.5 \) (s, Ar-C), 140.5 (s, Ar-C), 138.4 (s, Ar-C), 125.0 (d, Ar-CH), 124.0 (s, Ar-C=CH\(_2\)), 112.8 (d, Ar-CH), 109.6 (d, Ar-CH), 104.5 (t, Ar-C=CH\(_2\)), 73.1 [d, ArCH(CH\(_3\))O], 69.1 [t, ArCH(CH\(_3\))OCH\(_2\)], 55.3 (q, Ar-OCH\(_3\)), 21.0 [q, ArCH(CH\(_3\))O] ppm.

**HR-MS (APCI\(^+\))**: m/z calculated for [C\(_{12}\)H\(_{14}\)O\(_2\)]\(^+\)=[M]\(^+\): 190.0988; found 190.0980.

GP-3 was carried out with the 2-bromobenzyl alcohol 21n (100 mg, 0.30 mmol), allyl bromide (72.2 mg, 0.60 mmol) and NaH (28.8 mg, 1.20 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room
temperature, were added Pd(OAc)$_2$ (6.7 mg, 10 mol%), PPh$_3$ (15.6 mg, 20 mol%) and triethylbenzylammonium chloride (67 mg, 0.30 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 97:3) furnished the isochromene 28g' (28.0 mg, 32%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), $R_f$(21n)=0.15, $R_f$(28g')=0.65, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{max}$=2959, 2922, 2851, 1643, 1604, 1510, 1454, 1383, 1362, 1300, 1203, 1165, 1056, 1016, 856, 809, 738, 697 cm$^{-1}$.

**$^1$H-NMR (CDCl$_3$, 400 MHz):** $\delta$=7.45 (d, 2H, $J=7.3$ Hz, Ar-H), 7.37 (d, 1H, $J=7.3$ Hz, Ar-H), 7.35 (d, 1H, $J=7.3$ Hz, Ar-H), 7.29 (t, 1H, $J=7.3$ Hz, Ar-H), 6.68 (s, 1H, Ar-H), 6.60 (s, 1H, Ar-H), 6.10 [q, 1H, $J=1.5$ Hz, ArC(Me)=CHOCH$_2$], 5.14 (s, 2H, ArCH$_2$), 5.07 [q, 1H, $J=6.4$ Hz, Ar-CH(CH$_3$)], 3.87 (s, 3H, Ar-OCH$_3$), 1.80 (d, 3H, $J=1.5$ Hz, CH=CC(CH$_3$)$_3$), 1.54 [d, 3H, $J=6.4$ Hz, Ar-CH(CH$_3$)] ppm.

**$^{13}$C-NMR (CDCl$_3$, 100 MHz):** $\delta$=148.6 (s, Ar-C), 147.7 (s, Ar-C), 139.4 [d, Ar(CH$_3$)C=CH], 137.3 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 126.3 (s, Ar-C), 125.0 (s, Ar-C), 110.1 (s, ArC=CH$_2$), 108.2 (d, Ar-CH), 108.0 (d, Ar-CH), 73.1 [d, ArCH(CH$_3$)], 71.5 (t, Ar-CH$_2$), 56.4 (q, Ar-OCH$_3$), 19.7 [q, Ar(CH$_3$)C=CH], 13.2 [q, Ar(CH$_3$)CHO] ppm.

**HR-MS (APCI$^+$):** m/z calculated for [C$_{19}$H$_{21}$O$_3$]$^+$_=[M+H]$^+$: 297.1485; found 297.1477.

![Image of 28g](image-url)

**6-(Benzyloxy)-7-methoxy-1-methyl-4-methylene-3,4-dihydro-1H-isochromene (28g):**

Further elution of the column (petroleum ether/ethyl acetate, 97:3 to 90:10) yielded the isochromene 28g (40 mg, 45%). [TLC control (petroleum ether/ethyl acetate 85:15), $R_f$(21n)=0.15, $R_f$(28g)=0.55, UV detection].
IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \(\nu_{\text{max}}\)=2922, 2851, 1600, 1510, 1455, 1320, 1280, 1260, 1168, 1076, 747, 697 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta=7.46\) (d, 2H, \(J=7.3\) Hz, Ar-H), 7.38 (d, 1H, \(J=7.3\) Hz, Ar-H), 7.36 (d, 1H, \(J=7.3\) Hz, Ar-H), 7.31 (t, 1H, \(J=7.3\) Hz, Ar-H), 7.15 (s, 1H, Ar-H), 6.58 (s, 1H, Ar-H), 5.28 (s, 1H, ArC=CH\(_2\)A), 5.16 (s, 2H, Ar-CH\(_2\)), 4.85 (s, 1H, ArC=CH\(_2\)B), 4.85 [q, 1H, \(J=6.4\) Hz, ArCH(CH\(_3\))OCH\(_2\)], 4.48 [d, 1H, \(J=13.2\) Hz, ArCH(Me)OC\(_2\)H\(_2\)A], 4.30 [d, 1H, \(J=13.2\) Hz, ArCH(Me)OCH\(_2\)B], 3.88 (s, 3H, Ar-OCH\(_3\)), 1.53 [d, 3H, \(J=6.4\) Hz, ArCH(CH\(_3\))O] ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta=150.1\) (s, Ar-C), 147.2 (s, Ar-C), 138.5 (s, Ar-C), 137.0 (s, Ar-C), 132.7 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 123.6 (s, ArC=CH\(_2\)), 108.9 (d, Ar-CH), 107.7 (d, Ar-CH), 104.6 (t, ArC=CH\(_2\)), 72.8 [d, ArCH(CH\(_3\))OCH\(_2\)], 71.2 (t, ArCH\(_2\)O), 68.9 [t, ArCH(Me)OCH\(_2\)], 56.0 (q, Ar-OCH\(_3\)), 21.2 [q, ArCH(CH\(_3\))O] ppm.

HR-MS (APCI\(^{+}\)): m/z calculated for [C\(_{19}\)H\(_{20}\)NaO\(_3\)]\(^{+}\)=[M+Na]\(^{+}\): 319.1305; found 319.1305.

II.4.2 SYNTHESIS OF 2-BENZOXEPINONES:

General Procedure for the Sequential One-pot formation of Benzoxepinones (GP-1):

In an oven dried Schlenk tube, were added the 2-bromobenzyl alcohol 21 (100.0 mg, 0.31–0.53 mmol), ethyl acrylate [155.1–265.3 mg (i.e., 1.55–2.65 mmol)] and Cs\(_2\)CO\(_3\) [303.0–518.0 mg (i.e., 0.93–1.59mmol)] followed by the addition of toluene (2 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 50 °C in an oil bath for 48 h. After the completion of Michael addition (monitored by TLC) and to the cooled reaction mixture at room temperature, were added Pd(OAc)\(_2\) (6.9–11.9 mg, 10 mol%) and PPh\(_3\) (16.3–27.8 mg, 20 mol%) under nitrogen atmosphere. The reaction mixture was then heated at 80 °C in an oil bath for 24 h. Once after formation intermolecular Heck coupling product, (monitored by TLC) and then to the cooled reaction mixture at room temperature, was added DMF (3 mL) and heated to 120 °C, in an oil bath
for 12 h (monitored by TLC). The reaction mixture at room temperature was quenched by the addition of aqueous NH₄Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the lactenones 34 (40–48%).

**X-ray crystal structure data for the 8-methoxy-2-benzoxepin-3(1H)-one (34c):**

CCDC 930424

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**Tert-butyl (2E)-3-[2-[1-(3-tert-butoxy-3-oxopropoxy)ethyl]phenyl]acrylate (23z):**

In an oven dried Schlenk tube, were added the 2-bromobenzyl alcohol 21k (200.0 mg, 0.99 mmol), tertiarybutyl acrylate (637.0 mg, 4.97 mmol) and Cs₂CO₃ (972.0 mg, 2.98 mmol) followed by addition of toluene (4 mL) at room temperature under nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (22.0 mg, 10 mol%) and PPh₃ (52.0 mg, 20 mol%) under nitrogen
atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. Then, the mixture was cooled to room temperature, treated with aqueous NH₄Cl solution and then extracted with CH₂Cl₂ (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 90:10) furnished the diester 23z (220.0 mg, 59%) as yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 90:10), Rf(21k) = 0.35, Rf(23z) = 0.45, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νmax=2922, 1730, 1709, 1632, 1367, 1319, 1149, 1105, 954, 762 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.98 (d, 1H, J=15.6 Hz, CH=CHCOO’Bu), 7.52 (d, 1H, J=7.3 Hz, Ar-H), 7.48 (d, 1H, J=7.8 Hz, Ar-H), 7.38 (dd, 1H, J=7.8 and 7.3 Hz, Ar-H), 7.25 (dd, 1H, J=7.8 and 7.8 Hz, Ar-H), 6.27 (d, 1H, J=15.6 Hz, CH=CHCOO’Bu), 4.81 (q, 1H, J=6.4 Hz, Ar-CHCH₃), 3.55 (t, 2H, J=6.4 Hz, OCH₂CH₂COO’Bu), 2.48 (td, 2H, J=6.4 and 1.5 Hz, OCH₂CH₂COO’Bu), 1.55 [s, 9H, OC(CH₃)₃], 1.45 [s, 9H, OC(CH₃)₃], 1.40 (d, 3H, J=6.4 Hz, Ar-CHCH₃) ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=170.8 (s, O=C–O), 166.1 (s, O=C–O), 142.8 (s, Ar-C), 140.3 (d, CH=CHCOO’Bu), 132.4 (s, Ar-C), 130.0 (d, Ar-CH), 127.3 (d, Ar-CH), 126.6 (d, Ar-CH), 126.0 (d, Ar-CH), 122.0 (d, CH=CHCOO’Bu), 80.5 [s, OC(CH₃)₃], 80.4 [s, OC(CH₃)₃], 74.7 (d, Ar-CHCH₃), 64.5 (t, OCH₂CH₂COO’Bu), 36.4 (t, CH₂CH₂COO’Bu), 28.1 [q, 3C, OC(CH₃)₃], 28.0 [q, 3C, OC(CH₃)₃], 23.7 (q, Ar-CHCH₃) ppm.

HR-MS (APCI⁺): m/z calculated for [C₂₂H₃₁O₅]⁺=[M–H]⁺: 375.2166; found 375.2171.

![Ethyl (2E)-3-{2-[1-(3-ethoxy-3-oxopropoxy)ethyl]-4-methoxyphenyl]acrylate (23aa):](image-url)
In an oven dried Schlenk tube, were added the 2-bromobenzyl alcohol 211 (200.0 mg, 0.86 mmol), ethyl acrylate (433.0 mg, 4.32 mmol) and Cs₂CO₃ (846.0 mg, 2.58 mmol) followed by addition of toluene (4 mL) at room temperature under a nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (19.4 mg, 10 mol%) and PPh₃ (45.0 mg, 20 mol%) under nitrogen atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. Then, the mixture was cooled to room temperature, treated with aqueous NH₄Cl solution and then extracted with CH₂Cl₂ (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 85:15) furnished the diester 23aa (200.0 mg, 57%) as a yellow viscous oil.

[TLC control (petroleum ether/ethyl acetate 80:20), \( R_f(211)=0.45, R_f(23aa)=0.45 \), UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{max}=2923, 1735, 1712, 1631, 1603, 1493, 1252, 1179, 1162, 1107, 1034, 731 \text{ cm}^{-1} \).

\(^1\)H-NMR (CDCl₃, 400 MHz): \( \delta=7.94 \text{ (d, 1H, } J=15.6 \text{ Hz, CH=CHCOOEt), 7.50 \text{ (d, 1H, } J=8.3 \text{ Hz, Ar-H), 7.02 \text{ (d, 1H, } J=2.4 \text{ Hz, Ar-H), 6.79 \text{ (dd, 1H, } J=8.3 \text{ Hz and 2.4 Hz, Ar-H), 6.23 \text{ (d, 1H, } J=15.6 \text{ Hz, CH=CHCOOEt), 4.80 \text{ (q, 1H, } J=6.4 \text{ Hz, Ar-CHCH₃}, 4.24 \text{ (q, 2H, } J=7.3 \text{ Hz, OCH₂CH₃), 4.12 \text{ (qd, 2H, } J=7.3 \text{ and 1.9 Hz, OCH₂CH₃), 3.83 \text{ (s, 3H, Ar-OCH₃), 3.70–3.45 (m, 2H, OCH₂CH₂COOEt), 2.56 (t, 2H, } J=6.8 \text{ Hz, OCH₂CH₂COOEt), 1.37 (d, 3H, } J=6.4 \text{ Hz, Ar-CHCH₃), 1.31 (t, 3H, } J=7.3 \text{ Hz, OCH₂CH₃), 1.23 (t, 3H, } J=7.3 \text{ Hz, OCH₂CH₃) ppm.} \)

\(^{13}\)C-NMR (CDCl₃, 100 MHz): \( \delta=171.4 \text{ (s, O=C–O), 167.1 (s, O=C–O), 161.5 (s, Ar-C), 145.0 (s, Ar-C), 140.5 (d, CH=CHCOOEt), 128.2 (d, Ar-CH), 124.6 (s, Ar-C), 117.7 (d, CH=CHCOOEt), 113.6 (d, Ar-CH), 110.7 (d, Ar-CH), 74.7 (d, ArCHCH₃), 64.3 (t, OCH₂CH₂COOEt), 60.4 (t, OCH₂CH₃), 60.3 (t, OCH₂CH₃), 55.3 (q, Ar-OCH₃), 35.2 (t, OCH₂CH₂COOEt), 23.9 (q, ArCHCH₃), 14.3 (q, OCH₂CH₃), 14.1 (q, OCH₂CH₃) ppm.} \)
HR-MS (APCI⁺): m/z calculated for [C_{19}H_{26}NaO_6]^+=[M+Na]^+: 373.1622; found 373.1630.

Ethyl (2E)-3-[6-[1-(3-ethoxy-3-oxopropoxy)ethyl]-1,3-benzodioxol-5-yl]acrylate (23ab):

In an oven dried Schlenk tube, were added the 2-bromobenzyl alcohol 21m (200.0 mg, 0.82 mmol), ethyl acrylate (408.0 mg, 4.10 mmol) and Cs₂CO₃ (798.0 mg, 2.46 mmol) followed by addition of toluene (4 mL) at room temperature under a nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added Pd(OAc)₂ (18.0 mg, 10 mol%) and PPh₃ (42.0 mg, 20 mol%) under nitrogen atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. Then, the mixture was cooled to room temperature, treated with aqueous NH₄Cl solution and then extracted with CH₂Cl₂ (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 85:15) furnished the diester 23ab (178.0 mg, 60%) as a yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(21m)=0.50, R_f(23ab)=0.50, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): ν_max=2958, 2921, 2852, 1732, 1618, 1482, 1285, 1254, 1180, 1103, 1038, 934 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.92 (d, 1H, J=15.6 Hz, CH=CHCOOEt), 6.99 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 6.20 (d, 1H, J=15.6 Hz, CH=CHCOOEt), 5.98 (d, 1H, J=6.4 Hz, OCH₂O), 5.97 (d, 1H, J=6.4 Hz, Ar-H), 4.79 (q, 1H, J=6.8 Hz, Ar-CHCH₃), 4.24 (q, 2H, J=7.3 Hz, OCH₂CH₃), 4.14 (q, 2H, J=7.3 Hz, OCH₂CH₃), 3.65–3.50 (m, 2H, OCH₂CH₂COOEt), 2.55 (t, 2H, J=6.4 Hz,
OCH$_2$CH$_2$COOEt), 1.34 (d, 3H, $J=$6.8 Hz, Ar-CH$_2$), 1.32 (t, 3H, $J=$7.3 Hz, OCH$_2$CH$_3$), 1.25 (t, 3H, $J=$7.3 Hz, OCH$_2$CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta=$171.5 (s, O=C‒O), 167.0 (s, O=C‒O), 149.9 (s, Ar-C), 147.2 (s, Ar-C), 140.3 (d, CH=CHCOOEt), 138.9 (s, Ar-C), 125.8 (s, Ar-C), 118.2 (d, CH=CHCOOEt), 106.1 (d, Ar-CH), 105.6 (d, Ar-CH), 101.4 (t, OCH$_2$O), 74.1 (d, ArCHCH$_3$), 64.2 (t, OCH$_2$CH$_2$COOEt), 60.5 (t, OCH$_2$CH$_3$), 60.4 (t, OCH$_2$CH$_3$), 35.3 (t, OCH$_2$CH$_2$COOEt), 24.0 (q, ArCHCH$_3$), 14.3 (q, OCH$_2$CH$_3$), 14.2 (q, OCH$_2$CH$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{19}$H$_{25}$O$_7$]$^+=[M+H]$^+$: 365.1595; found 365.1603.

Ethyl (2E)-3-[2-(hydroxymethyl)-4,5-dimethoxyphenyl]acrylate (33g):

To a cold (–78 °C), magnetically stirred solution of the diester 23g (80 mg, 0.22 mmol), under argon atmosphere, in dry toluene (2.5 mL), was added 1M solution of NaHMDS (1.1 mL, 1.1 mmol) in toluene. Then the reaction mixture was allowed to stir at –78 °C for 1.5 h followed by at –10 °C for 0.5 h. The reaction mixture was quenched with aqueous NH$_4$Cl solution and extracted with ethyl acetate (3 x 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na$_2$SO$_4$), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 70:30 to 50:50) furnished the hydroxy ester (39.6 mg, 69%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), $R_f$(23g)=0.40, $R_f$(33g)=0.25, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=3485, 2937, 1703, 1629, 1270, 1171, 1103, 1033, 859 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta=$7.95 (d, 1H, $J=$15.6 Hz, CH=CHCOOEt), 7.07 (s, 1H, Ar-H), 6.95 (s, 1H, Ar-H), 6.29 (d, 1H, $J=$15.6 Hz, CH=CHCOOEt), 4.78 (s, 2H, Ar-CH$_2$OH), 4.24 (q, 2H, $J=$7.3 Hz, OCH$_2$CH$_3$), 3.90 (s, 3H, Ar-OCCH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 1.89 (br. s, OH), 1.32 (t, 3H, $J=$7.3 Hz, OCH$_2$CH$_3$) ppm.
$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$=167.2 (s, O=C–O), 150.8 (s, Ar-C), 148.6 (s, Ar-C), 140.8 (d, CH=CHCOOEt), 133.5 (s, Ar-C), 125.1 (s, Ar-C), 117.6 (d, Ar-CH), 111.5 (d, Ar-CH), 108.9 (d, CH=CHCOOEt), 62.3 (t, Ar-CH$_2$OH), 60.5 (t, OCH$_2$CH$_3$), 55.9 (q, 2C, 2 $\times$ Ar-OCH$_3$), 14.3 (q, OCH$_2$CH$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{14}$H$_{18}$NaO$_5$]$^+$$=[M+Na]^+$: 289.1046; found 289.1057.

**Tert-butyl (2E)-3-[2-(hydroxymethyl)-4,5-dimethoxyphenyl]acrylate (33s):**

To a cold (–78 °C), magnetically stirred solution of the diester 23s (100 mg, 0.24 mmol), under argon atmosphere, in dry toluene (2 mL), was added 1M solution of NaHMDS (0.96 mL, 0.96 mmol) in toluene. Then the reaction mixture was allowed to stir at –78 °C for 1 h and allowed to –10 °C for 3 h. The reaction mixture was quenched with aqueous NH$_4$Cl solution and extracted with ethyl acetate (3 $\times$ 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na$_2$SO$_4$), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 70:30 to 50:50) furnished the hydroxy ester 33s (43.4 mg, 62%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), R$_f$(23s)=0.50, R$_f$(33s)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}$=3432, 2975, 1702, 1629, 1514, 1457, 1274, 1146, 1104, 977, 845 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$=7.87 (d, 1H, $J$=15.6 Hz, CH=CHCOO‘Bu), 7.07 (s, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.22 (d, 1H, $J$=15.6 Hz, CH=CHCOO‘Bu), 4.78 (s, 2H, Ar-CH$_2$OH), 3.90 (s, 3H, Ar-OCH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 1.89 (br. s, OH), 1.52 [(s, 9H, C(CH$_3$)$_3$] ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$=166.6 (s, O=C-O), 150.6 (s, Ar-C), 148.6 (s, Ar-C), 139.8 (d, CH=CHCOO‘Bu), 133.4 (s, Ar-C), 125.3 (s, Ar-C), 119.6 (d,
Ethyl (5,6-dimethoxy-1,3-dihydro-2-benzofuran-1-yl)acetate (22g):

In an oven dried Schlenk tube, were added the diester 23g (50.0 mg, 0.14 mmol) and Cs$_2$CO$_3$ (133.5 mg, 0.72 mmol) followed by the addition of toluene (2 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 120 °C in an oil bath for 24 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH$_4$Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na$_2$SO$_4$), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 85:15) furnished the cyclic ether 22g (5.6 mg, 16%), as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 75:25), $R_f(23g) = 0.45$, $R_f(22g) = 0.46$, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{\text{max}} = 2917, 1728, 1602, 1505, 1464, 1266, 1220, 1163, 1107, 1037, 855, 729$ cm$^{-1}$.  

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta = 6.72$ (s, 1H, Ar-H), 6.70 (s, 1H, Ar-H), 5.65–5.55 (m, 1H, ArCH$_2$COOEt), 5.08 (dd, 1H, $J = 11.7$ and 2.9 Hz, ArCH$_2$H$_2$O), 5.00 (dd, 1H, $J = 11.7$ and 1.5 Hz, ArCH$_2$H$_2$O), 4.18 (q, 2H, $J = 7.3$ Hz, OCH$_2$CH$_3$), 3.86 (s, 3H, ArOCH$_3$), 3.85 (s, 3H, ArOCH$_3$), 2.72 (dd, 2H, $J = 7.3$ and 6.4 Hz, ArCHCH$_2$COOEt), 1.25 (t, 3H, $J = 7.3$ Hz, OCH$_2$CH$_3$) ppm.  

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta = 170.9$ (s, O=–C=O), 149.3 (s, Ar-C), 148.9 (s, Ar-C), 132.2 (s, Ar-C), 130.6 (s, Ar-C), 104.2 (d, Ar-CH), 103.9 (d, Ar-CH), 80.6
(d, ArCHCH₂COOEt), 72.8 (t, ArCH₂O), 60.6 (t, OCH₂CH₃), 56.1 (q, Ar-OCH₃),
56.0 (q, Ar-OCH₃), 41.8 (t, ArCHCH₂COOEt), 14.2 (q, OCH₂C₃H₇) ppm.

**HR-MS (APCI⁺):** m/z calculated for [C₁₄H₁₈NaO₅]⁺=[M+Na]⁺: 289.1046; found 289.1052.

**Tert-butyl (5,6-dimethoxy-1,3-dihydro-2-benzofuran-1-yl)acetate (22s):**

In an oven dried Schlenk tube, were added the diester 23s (50.0 mg, 0.12 mmol) and Cs₂CO₃ (117.3 mg, 0.36 mmol) followed by the addition of CH₃CN (3 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 80 °C in an oil bath for 24 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH₄Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the cyclic ether 22s (5.9 mg, 16%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), Rf(23s)=0.45, Rf(22s)=0.47, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νmax=2975, 1723, 1603, 1503, 1464, 1391, 1274, 1220, 1146, 1108, 1036, 844, 766 cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** δ=6.71 (2 × s, 2H, Ar-H), 5.60–5.48 (m, 1H, ArCHCH₂COO'Bu), 5.06 (dd, 1H, J=11.7 and 2.9 Hz, ArCH₂H₃O), 4.98 (dd, 1H, J=11.7 and 1.5 Hz, ArCH₃H₆O), 3.85 (s, 3H, ArOCH₃), 3.84 (s, 3H, ArOCH₃), 2.65 (dd, 2H, J=6.8 and 1.5 Hz, ArCHCH₂COOEt), 1.44 [s, 9H, OC(CH₃)₃] ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** δ=170.2 (s, O=C–O), 149.2 (s, Ar-C), 148.8 (s, Ar-C), 132.6 (s, Ar-C), 130.7 (s, Ar-C), 104.3 (d, Ar-CH), 103.9 (d, Ar-CH), 80.8 [s, OC(CH₃)₃], 80.7 (d, ArCHCH₂COO'Bu), 72.8 (t, ArCH₂O), 56.1 (q, Ar-OCH₃), 56.0 (q, Ar-OCH₃), 42.9 (t, ArCHCH₂COOEt), 28.0 [q, 3C, OC(CH₃)₃] ppm.
HR-MS (APCI\(^+\)): m/z calculated for [C\(_{16}H_{20}O_{4}\)]\(^+\)=[M–(H\(_2\)O)]\(^+\): 276.1356; found 276.1352.

\[ \text{HRMS (APCI\(^+\))} \]

2-Benzoepin-3(1\(H\))-one (34a):

GP-1 was carried out with the 2-bromobenzyl alcohol 21a (100.0 mg, 0.53 mmol), ethyl acrylate (265.3 mg, 2.65 mmol), Cs\(_2\)CO\(_3\) (518.0 mg, 1.59 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with Pd(OAc)\(_2\) (11.9 mg, 10 mol%), PPh\(_3\) (27.8 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the lactenone 34a (39.5 mg, 46%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), \(R_f(21a)=0.50, R_f(34a)=0.38\), UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \(\nu_{\text{max}}\)=2921, 1707, 1602, 1457, 1273, 1209, 1157, 1106, 1034, 818, 741 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta=7.55–7.30\) (m, 4H, Ar-H), 7.21 (d, 1H, \(J=11.7\) Hz, \(CH=CHCO\)), 6.35 (d, 1H, \(J=11.7\) Hz, \(CH=CHCO\)), 5.06 (s, 2H, ArCH\(_2\)O) ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta=167.6\) (s, O=C–O), 140.6 (d, CH=CHCO), 135.4 (s, Ar-C), 135.1 (s, Ar-C), 130.2 (d, Ar-CH), 129.8 (d, Ar-CH), 129.7 (d, Ar-CH), 128.6 (d, Ar-CH), 122.7 (d, CH=CHCO), 68.6 (t, ArCH\(_2\)O) ppm. HR-MS (APCI\(^+\)) m/z calculated for [C\(_{10}H_{7}O\)]\(^+\)=[(M+H)–H\(_2\)O]\(^+\): 143.0491; found 143.0496.

8-(Benzyloxy)-2-benzoepin-3(1\(H\))-one (34b):

GP-1 was carried out with the 2-bromobenzyl alcohol 21b (100.0 mg, 0.34 mmol), ethyl acrylate (170.2 mg, 0.17 mmol), Cs\(_2\)CO\(_3\) (332.3 mg, 1.03 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with Pd(OAc)\(_2\) (7.6 mg,
10 mol%), PPh₃ (17.8 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 85:15) furnished the lactenone 34b (36.2 mg, 40%) as a pale yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(21b)=0.48, R_f(34b)=0.41, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): ν_max=2925, 1701, 1605, 1501, 1283, 1178, 1040, 835, 737 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.46–7.30 (m, 6H, Ar-H), 7.14 (d, 1H, J=12.2 Hz, CH=CHCO), 7.03 (dd, 1H, J=8.3 and 2.4 Hz, Ar-H), 7.01 (d, 1H, J=2.4 Hz, Ar-H), 6.22 (d, 1H, J=12.2 Hz, CH=CHCO), 5.12 (s, 2H, PhCH₂O), 5.00 (s, 2H, ArCH₂O) ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=168.0 (s, O=C–O), 160.1 (s, Ar-C), 140.6 (d, CH=CHCO), 137.1 (s, Ar-C), 136.0 (s, Ar-C), 131.7 (d, Ar-CH), 128.7 (d, 2C, Ar-CH), 128.5 (s, Ar-C), 128.3 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 120.2 (d, CH=CHCO), 115.7 (d, Ar-CH), 115.1 (d, Ar-CH), 70.3 (t, PhCH₂O), 68.7 (t, ArCH₂O) ppm.

HR-MS (APCI⁺): m/z calculated for [C₁₇H₁₅O₃]⁺=[M+H]⁺: 267.1016; found 267.1020.

8-Methoxy-2-benzoxepin-3(1H)-one (34c):

GP-1 was carried out with the 2-bromobenzyl alcohol 21c (100.0 mg, 0.46 mmol), ethyl acrylate (230.3 mg, 2.30 mmol), Cs₂CO₃ (449.6 mg, 1.38 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with Pd(OAc)₂ (10.3 mg, 10 mol%), PPh₃ (24.1 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the lactenone 34c (40.4 mg, 46%) as a pale brown solid, recrystallized from
dichloromethane/hexane (m. p. 96–98 °C). [TLC control (petroleum ether/ethyl acetate 80:20), \( R_f(21c)=0.45, R_f(34c)=0.40, \) UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \( \nu_{max}=2926, 1699, 1605, 1503, 1453, 1284, 1251, 1160, 1034, 909, 805, 727 \text{ cm}^{-1} \).

**\(^1\)H-NMR (CDCl\(_3\), 400 MHz)**: \( \delta=7.34 \text{ (d, 1H, } J=8.3 \text{ Hz, Ar-H)}, 7.14 \text{ (d, 1H, } J=12.2 \text{ Hz, } CH=CHCO), 6.96 \text{ (dd, 1H, } J=8.3 \text{ and } 2.4 \text{ Hz, Ar-H)}, 6.92 \text{ (d, 1H, } J=2.4 \text{ Hz, Ar-H}), 6.21 \text{ (d, 1H, } J=12.2 \text{ Hz, } CH=CHCO), 5.01 \text{ (s, 2H, ArCH}\_2\text{O), 3.85 (s, 3H, Ar-OCH}\_3\text{) ppm.} \)

**\(^1\)C-NMR (CDCl\(_3\), 100 MHz)**: \( \delta=168.1 \text{ (s, O=C‒O), 161.0 (s, Ar-C), 140.7 (d, } CH=CHCO), 137.0 \text{ (s, Ar-C), 131.7 (d, Ar-CH), 128.3 (s, Ar-C), 120.0 (d, } CH=CHCO), 114.8 \text{ (d, Ar-CH), 114.2 (d, Ar-CH), 68.7 (t, ArCH}\_2\text{O), 55.5 (q, Ar-OCH}\_3\text{) ppm.} \)

**HR-MS (APCI\(^+\)**): m/z calculated for \([C_{11}H_{11}O_3]^+=[M+H]^+\): 191.0703; found 191.0704.

![34d](image)

**8-(Benzyloxy)-7-methoxy-2-benzoxepin-3(1H)-one (34d)**:

**GP-1** was carried out with the 2-bromobenzyl alcohol 34d (100.0 mg, 0.31 mmol), ethyl acrylate (155.2 mg, 1.55 mmol), Cs\(_2\)CO\(_3\) (303.0 mg, 0.93 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with Pd(OAc)\(_2\) (6.9 mg, 10 mol%), PPh\(_3\) (16.3 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the lactenone 34d (38.6 mg, 42%) as white solid, recrystallized from dichloromethane/hexane (m. p. 159–160 °C). [TLC control (petroleum ether/ethyl acetate 75:25), \( R_f(21d)=0.45, R_f(34d)=0.38, \) UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \( \nu_{max}=2924, 1702, 1603, 1519, 1368, 1275, 1165, 1025, 740 \text{ cm}^{-1} \).
\(^1\text{H-NMR (CDCl}_3, 400 \text{ MHz)}: \delta=7.42 \,(d, \,2\,H, \,J=7.8 \,\text{Hz, Ar-H}), \,7.38 \,(dd, \,2\,H, \,J=7.8 \,\text{and} \,7.3 \,\text{Hz, Ar-H}, \,7.32 \,(t, \,1\,H, \,J=7.3 \,\text{Hz, Ar-H}), \,7.11 \,(d, \,1\,H, \,J=12.2 \,\text{Hz, CH}=\text{CHCO}), \,6.91 \,(s, \,1\,H, \,Ar-H), \,6.89 \,(s, \,1\,H, \,Ar-H), \,6.25 \,(d, \,1\,H, \,J=12.2 \,\text{Hz, CH}=\text{CHCO}), \,5.20 \,(s, \,2\,H, \,PhCH}_2\text{O}), \,4.92 \,(s, \,2\,H, \,ArCH}_2\text{O}), \,3.91 \,(s, \,3\,H, \,Ar-OCH}_3) \text{ppm.}

\(^{13}\text{C-NMR (CDCl}_3, 100 \text{ MHz)}: \delta=167.9 \,(s, \,O=C‒O), \,150.3 \,(s, \,Ar-C), \,149.5 \,(s, \,Ar-C), \,140.5 \,(d, \,CH=\text{CHCO}), \,136.2 \,(s, \,Ar-C), \,129.0 \,(s, \,Ar-C), \,128.7 \,(d, \,2\,C, \,Ar-CH), \,128.6 \,(s, \,Ar-C), \,128.2 \,(d, \,Ar-CH), \,127.2 \,(d, \,2\,C, \,Ar-CH), \,121.0 \,(d, \,CH=\text{CHCO}), \,113.7 \,(d, \,Ar-CH), \,112.7 \,(d, \,Ar-CH), \,71.1 \,(t, \,PhCH}_2\text{O), \,68.3 \,(t, \,ArCH}_2\text{O}), \,56.2 \,(q, \,Ar-OCH}_3) \text{ppm.}

\text{HR-MS (APCI}^+)\text{: m/z calculated for }[\text{C}_{18}\text{H}_{17}\text{O}_4]^+=[\text{M+H}]^+: 297.1121; \text{found 297.1121.}

\text{7-(Benzyloxy)-8-methoxy-2-benzoxepin-3(1H)-one (34e):}

\text{GP-1 was carried out with the 2-bromobenzyl alcohol 21e (100.0 mg, 0.31 mmol), ethyl acrylate (155.2 mg, 1.55 mmol), Cs}_2\text{CO}_3 \,(303.0 \text{mg, 0.93 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with Pd(OAc)}_2 \,(6.9 \text{mg, 10 mol%), PPh}_3 \,(16.3 \text{mg, 20 mol%}) \text{for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the lactenone 34e (40.5 mg, 44%) as colorless solid, recrystallized from dichloromethane/petroleum ether (m. p. 160–161 °C). [TLC control (petroleum ether/ethyl acetate 75:25), R}_2\text{R(21e)=0.45, R}_2\text{R(34e)=0.38, UV detection].}

\text{IR (neat; MIR-ATR, 4000–600 cm}^-1\text{: }\nu_{\text{max}}=2925, \,1694, \,1602, \,1517, \,1453, \,1354, \,1275, \,1164, \,1106, \,1031, \,987, \,864, \,733, \,698 \text{cm}^-1\text{.}

\(^1\text{H-NMR (CDCl}_3, 400 \text{ MHz)}: \delta=7.42 \,(d, \,2\,H, \,J=7.8 \,\text{Hz, Ar-H}), \,7.37 \,(dd, \,2\,H, \,J=7.8 \,\text{and} \,7.3 \,\text{Hz, Ar-H}, \,7.31 \,(t, \,1\,H, \,J=7.3 \,\text{Hz, Ar-H}), \,7.04 \,(d, \,1\,H, \,J=12.2 \,\text{Hz, CH}=\text{CHCO}), \,6.91 \,(s, \,1\,H, \,Ar-H), \,6.89 \,(s, \,1\,H, \,Ar-H), \,6.22 \,(d, \,1\,H, \,J=12.2 \,\text{Hz,}

CH=CHCO), 5.16 (s, 2H, PhCH₂O), 4.97 (s, 2H, ArCH₂O), 3.93 (s, 3H, Ar-OCH₃) ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** δ=168.0 (s, O=C‒O), 150.9 (s, Ar-C), 148.7 (s, Ar-C), 140.6 (d, CH=CHCO), 136.3 (s, Ar-C), 129.2 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.4 (s, Ar-C), 128.1 (d, Ar-CH), 127.2 (d, 2C, Ar-CH), 120.7 (d, CH=CHCO), 114.7 (d, Ar-CH), 111.7 (d, Ar-CH), 71.1 (t, PhCH₂O), 68.3 (t, ArCH₂O), 56.2 (q, Ar-OCH₃) ppm.

**HR-MS (APCI⁺):** m/z calculated for [C₁₈H₁₇O₄]⁺=[M+H]⁺: 297.1121; found 297.1120.

![4f]

[1,3]Dioxolo[4,5-h][2]benzoxepin-7(5H)-one (34f):

GP-1 was carried out with the 2-bromobenzyl alcohol 21f (100.0 mg, 0.43 mmol), ethyl acrylate (215.2 mg, 2.15 mmol), Cs₂CO₃ (423.0 mg, 1.30 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with Pd(OAc)₂ (9.6 mg, 10 mol%), PPh₃ (22.5 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the lactenone 34f (38.6 mg, 44%) as colorless solid, recrystallized from dichloromethane/petroleum ether (m. p. 149–150 °C). [TLC control (petroleum ether/ethyl acetate 80:20), Rₜ(21f)=0.45, Rₜ(34f)=0.40, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** ν_max=2921, 1698, 1617, 1504, 1490, 1387, 1267, 1238, 1147, 1023, 928, 879 cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** δ=7.06 (d, 1H, J=12.2 Hz, CH=CHCO), 6.86 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H), 6.24 (d, 1H, J=12.2 Hz, CH=CHCO), 6.03 (s, 2H, O-CH₂-O), 4.93 (s, 2H, ArCH₂O) ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** δ=167.8 (s, O=–C–O), 149.0 (s, Ar-C), 148.7 (s, Ar-C), 140.3 (d, CH=CHCO), 130.2 (s, Ar-C), 130.0 (s, Ar-C), 121.0 (d, CH=CHCO), 109.3 (d, Ar-CH), 109.0 (d, Ar-CH), 101.9 (t, O-CH₂-O), 68.2 (t, ArCH₂O) ppm.
HR-MS (APCI⁺): m/z calculated for [C_{11}H_{9}O_{4}]^+=[M+H]^+: 205.0495; found 205.0493.

![Image of 7,8-Dimethoxy-2-benzoxepin-3(H)-one (34g)](image)

**7,8-Dimethoxy-2-benzoxepin-3(1H)-one (34g):**

**GP-1** was carried out with the 2-bromobenzyl alcohol 21g (100.0 mg, 0.40 mmol), ethyl acrylate (202.6 mg, 2.02 mmol), Cs₂CO₃ (395.6 mg, 1.21 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with Pd(OAc)₂ (9.1 mg, 10 mol%), PPh₃ (21.0 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 70:30) furnished the lactenone 34g (42.8 mg, 48%) as yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 75:25), Rₚ(21g)=0.45, Rₚ(34g)=0.30, UV detection].

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** νₘₚₑₛ= 2924, 1693, 1603, 1519, 1463, 1356, 1274, 1247, 1164, 1107, 1029, 988, 840, 731 cm⁻¹.

**¹H-NMR (CDCl₃, 400 MHz):** δ=7.12 (d, 1H, J=12.2 Hz, CH=CHCO), 6.90 (s, 1H, Ar-H), 6.87 (s, 1H, Ar-H), 6.26 (d, 1H, J=12.2 Hz, CH=CHCO), 4.98 (s, 2H, ArCH₂O), 3.93 (s, 3H, ArOCH₃), 3.90 (s, 3H, ArOCH₃) ppm.

**¹³C-NMR (CDCl₃, 100 MHz):** δ=168.0 (s, O=C–O), 150.3 (s, Ar-C), 149.7 (s, Ar-C), 140.6 (d, CH=CHCO), 128.7 (s, Ar-C), 128.6 (s, Ar-C), 120.9 (d, CH=CHCO), 112.1 (d, Ar-CH), 111.3 (d, Ar-CH), 68.3 (t, ArCH₂O), 56.2 (q, ArOCH₃), 56.1 (q, ArOCH₃) ppm.

**HR-MS (APCI⁺):** m/z calculated for [C_{12}H_{13}O₄]⁺=[M+H]⁺: 221.0808; found 221.0804.
6,7,8-Trimethoxy-2-benzoxepin-3(1H)-one (34h):

GP-1 was carried out with the 2-bromobenzyl alcohol 21h (100.0 mg, 0.36 mmol), ethyl acrylate (180.7 mg, 1.80 mmol), Cs₂CO₃ (351.9 mg, 1.08 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with Pd(OAc)₂ (8.1 mg, 10 mol%), PPh₃ (18.9 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the lactenone 34h (42.3 mg, 47%) as yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), \( R_f \left( 21h \right) = 0.45, \ R_f \left( 34h \right) = 0.38, \) UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 2925, 1703, 1595, 1498, 1458, 1375, 1338, 1249, 1123, 1089, 1031, 822 \) cm⁻¹.

\(^1\)H-NMR (CDCl₃, 400 MHz): \( \delta = 7.43 \) (d, 1H, \( J = 12.2 \) Hz, \( CH=CHCO \)), 6.71 (s, 1H, Ar-H), 6.24 (d, 1H, \( J = 12.2 \) Hz, \( CH=CHCO \)), 4.94 (s, 2H, ArCH₂O), 3.91 (s, 3H, ArOCH₃), 3.90 (s, 3H, ArOCH₃), 3.87 (s, 3H, ArOCH₃) ppm.

\(^1^3\)C-NMR (CDCl₃, 100 MHz): \( \delta = 168.2 \) (s, O=C--O), 155.0 (s, Ar-C), 152.2 (s, Ar-C), 142.5 (s, Ar-C), 135.6 (d, CH=CHCO), 131.9 (s, Ar-C), 122.6 (s, Ar-C), 120.2 (d, CH=CHCO), 107.4 (d, Ar-CH), 68.7 (t, ArCH₂O), 61.7 (q, Ar-OCH₃), 61.0 (q, Ar-OCH₃), 56.2 (q, Ar-OCH₃) ppm.

HR-MS (APCI⁺): m/z calculated for \([C_{13}H_{15}O_5]^+ = [M+H]^+\): 251.0914; found 251.0913.

1-Methyl-2-benzoxepin-3(1H)-one (34i):

In an oven dried Schlenk tube, were added the diester 23z (200.0 mg, 0.53 mmol) and Cs₂CO₃ (520.0 mg, 1.59 mmol) followed by the addition of DMF (4 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was
stirred at 120 °C in an oil bath for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH₄Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the lactenone 34i (50.8 mg, 55%) as yellow oil. [TLC control (petroleum ether/ethyl acetate 80:20), Rₛ(23z)=0.50, Rₛ(34i)=0.25, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νₘₚₐₓ=2923, 2852, 1701, 1617, 1455, 1398, 1269, 1215, 1152, 1068, 1044, 1018, 972, 823, 808, 777, 731 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.60–7.30 (m, 4H, Ar-C), 7.21 (d, 1H, J=12.2 Hz, CH=CHCO), 6.39 (d, 1H, J=12.2 Hz, CH=CHCO), 5.31 [q, 1H, J=6.8 Hz, ArCH(CH₃)O], 1.85 [d, 3H, J=6.8 Hz, ArCH(CH₃)O] ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=167.4 (s, O=–C–O), 140.4 (d, CH=CHCO), 138.2 (s, Ar-C), 135.1 (s, Ar-C), 130.1 (d, Ar-CH), 129.9 (d, Ar-CH), 129.1 (d, Ar-CH), 124.9 (d, Ar-CH), 123.0 (d, CH=CHCO), 72.7 [d, ArCH(CH₃)O], 17.3 [q, ArCH(CH₃)O] ppm.


7,8-Dimethoxy-1-methyl-2-benzoxepin-3(1H)-one (34j):

In an oven dried Schlenk tube, were added the diester 23v (220.0 mg, 0.50 mmol) and Cs₂CO₃ (493.0 mg, 1.50 mmol) followed by the addition of DMF (4 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 120 °C in an oil bath for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH₄Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of
the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 70:30 to 60:40) furnished the lactenone 34j (62.5 mg, 52%) as yellow oil. [TLC control (petroleum ether/ethyl acetate 60:40), R(23v)=0.75, R(34j)=0.20, UV detection].

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νₘₐₓ=2925, 2852, 1695, 1604, 1518, 1462, 1362, 1335, 1199, 1177, 1151, 1068, 1025, 957, 863, 812, 729, 612 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=7.11 (d, 1H, J=12.2 Hz, CH=CHCO), 6.96 (s, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 6.30 (d, 1H, J=12.2 Hz, CH=CHCO), 5.25 [q, 1H, J=6.4 Hz, ArCH(CH₃)O], 3.95 (s, 3H, Ar-OCH₃), 3.90 (s, 3H, Ar-OCH₃) 1.83 [d, 3H, J=6.4 Hz, ArCH(CH₃)O] ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=167.7 (s, O=C–O), 150.3 (s, Ar-C), 149.2 (s, Ar-C), 140.2 (d, CH=CHCO), 131.9 (s, Ar-C), 128.3 (s, Ar-C), 121.4 (d, CH=CHCO), 112.3 (d, Ar-CH), 107.9 (d, Ar-CH), 72.4 [d, ArCH(CH₃)O], 56.1 (q, Ar-OCH₃), 56.0 (q, Ar-OCH₃), 17.5 [q, ArCH(CH₃)O] ppm.

HR-MS (APCI⁺): m/z calculated for [C₁₃H₁₅O₄]⁺=[M+H]⁺: 235.0695; found 235.0694.

8-Methoxy-1-methyl-2-benzoexepin-3(1H)-one (34k):

In an oven dried Schlenk tube, were added the diester 23aa (150.0 mg, 0.43 mmol) and Cs₂CO₃ (419.0 mg, 1.29 mmol) followed by the addition of DMF (3 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 120 °C in an oil bath for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH₄Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 80:20)
furnished the lactenone 34k (50.8 mg, 58%) as yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), \( R_f(23aa)=0.60, R_f(34k)=0.30 \), UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \( \nu_{\text{max}}=2923, 2852, 1697, 1605, 1562, 1501, 1460, 1399, 1382, 1236, 1218, 1178, 1073, 1035, 975, 876, 859 \text{ cm}^{-1} \).

\(^{1}\)H-NMR (CDCl\(_3\), 400 MHz): \( \delta=7.33 \text{ (d, } 1 \text{H, } J=8.3 \text{ Hz, Ar-H), 7.14 \text{ (d, } 1 \text{H, } J=11.7 \text{ Hz, } CH=CHCO), 7.00 \text{ (d, } 1 \text{H, } J=2.4 \text{ Hz, Ar-H), 6.94 \text{ (dd, } 1 \text{H, } J=8.3 \text{ and } 2.4 \text{ Hz, Ar-H), 6.25 \text{ (d, } 1 \text{H, } J=11.7 \text{ Hz, } CH=CHCO), 5.26 \text{ [q, } 1 \text{H, } J=6.8 \text{ Hz, ArCH(CH}_3\text{O)}), 3.87 \text{ (s, } 3 \text{H, Ar-OCH}_3\text{)} 1.82 \text{ [d, } 3 \text{H, } J=6.8 \text{ Hz, ArCH(CH}_3\text{O)] ppm.}

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \( \delta=167.8 \text{ (s, O=CHCO), 140.5 \text{ (d, } } CH=CHCO), 140.2 \text{ (s, Ar-C), 131.8 \text{ (d, Ar-CH), 128.0 \text{ (s, Ar-C), 120.5 \text{ (d, } } CH=CHCO), 113.6 \text{ (d, Ar-CH), 111.4 \text{ (d, Ar-CH), 72.5 \text{ [d, ArCH(CH}_3\text{O)}), 55.5 \text{ (q, Ar-OCH}_3\text{)} 17.3 \text{ [q, ArCH(CH}_3\text{O)] ppm.}

HR-MS (APCI\(^{+}\)): m/z calculated for [C\(_{12}\)H\(_{13}\)O\(_3\)]\(^{+}\)=[M+H]\(^{+}\): 205.0859; found 205.0862.

8,9-Dihydro[1,3]dioxolo[4,5-\(h\)][2]benzoxepin-7(5\(H\))-one (34l):

In an oven dried Schlenk tube, were added the diester 23ab (80.0 mg, 0.22 mmol) and Cs\(_2\)CO\(_3\) (214.0 mg, 0.66 mmol) followed by the addition of DMF (2 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 120 \(^{\circ}\)C in an oil bath for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH\(_4\)Cl and extracted with DCM (3 \times 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na\(_2\)SO\(_4\)), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the lactenone 34l (24.0 mg, 50%) as yellow oil. [TLC control (petroleum ether/ethyl acetate 80:20), \( R_f(23ab)=0.50, R_f(34l)=0.20 \), UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \( \nu_{\text{max}}=2921, 2851, 1694, 1505, 1489, 1385, 1261, 1156, 1036, 932 \text{ cm}^{-1} \).
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta = 7.06$ (d, 1H, $J=12.2$ Hz, $CH=CHCO$), 6.98 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H), 6.30 (d, 1H, $J=12.2$ Hz, CH=CHCO), 6.04 (d, 1H, $J=6.3$ Hz, OCH$_2$H$_3$O), 6.03 (d, 1H, $J=6.3$ Hz, OCH$_2$H$_3$O), 5.20 [q, 1H, $J=6.3$ Hz, ArCH(CH$_3$)O], 1.79 [d, 3H, $J=6.3$ Hz, ArCH(CH$_3$)O] ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta = 167.6$ (s, O=–O), 149.3 (s, Ar-C), 148.1 (s, Ar-C), 140.0 (d, CH=CHCO), 133.7 (s, Ar-C), 129.7 (s, Ar-C), 121.6 (d, CH=CHCO), 109.3 (d, Ar-CH), 105.6 (d, Ar-CH), 101.9 (t, OCH$_2$O), 72.3 (d, ArCHCH$_3$), 17.6 (q, ArCHCH$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{12}$H$_{11}$O$_4$]$^+=[(M+H)]$: 219.0652; found 219.0657.
CHAPTER III

SYNTHESIS

OF

ARYL-DIHYDRO-INDENOINDOLES

III. 1 INTRODUCTION:

One-pot synthetic trials have gained significance in synthetic organic chemistry, as they involve constructing more than one bond using a single operation\[^{53}\] and avoid intermediate isolation. Enhancement of such one-pot practices, which are useful in forming multiple C-C as well as C-heteroatom bonds, in particular, to construct complex molecular frame works and elegant biologically active natural products, are of immense interest. In this aspect, several synthetic methods based on a domino/sequential domino one-pot have been reported. For example, the use of multiple catalysts in one step either sequentially or together, a single catalytic system to catalyze multiple steps in a domino/sequential domino/tandem fashion and even an initial reaction mediated by the catalyst followed by in-situ treatment of a functionality which is generated in the first step by the addition of other reagents in stoichiometric quantities or vice versa, to promote subsequent simple and effective reactions.\[^{54,55}\] Most of these one-pot techniques were carried out in same medium for all transformations with respect to solvent, reagents, acid and/or base. In case of a few sequential one-pot processes, prior work-up was required in situations where complications occurred before the next reaction could be conducted. Domino sequential one-pot reactions without isolation of the intermediate are said to be telescoping syntheses. Since these one-pot techniques avoid the isolation of intermediate species, there is a substantial decrease in waste generation, in terms of minimal use of solvents and reagents, leading to
improvement of strategic efficiency. Most importantly, they save time over conventional step-wise operations, which has caused chemists to pay greater attention to the development of such procedures.\textsuperscript{91} Friedel-Crafts reaction and Fischer-indole synthesis are well-known classical and effective processes introduced by Friedel and Crafts in 1877\textsuperscript{92} and Fischer in 1883,\textsuperscript{93} respectively. The Fischer-indole synthesis lead to bio-active indole core commonly encountered in indole alkaloid natural products and in a few useful pharmaceuticals.\textsuperscript{94} For example, indole alkaloids like yuehchukene 1 a polycyclic bis-indole alkaloid, acts as a potential fertility-regulating agent,\textsuperscript{95} borreverine 2 shows antibacterial activity,\textsuperscript{96} paspaline 3 displays a potent tremorgenic activity\textsuperscript{97} and compounds 4 and 5 exhibit prostaglandin D\textsubscript{2} receptor antagonist activity (Figure III.1).\textsuperscript{98}

![Indole scaffolds](image)

**Figure III.1**

Indole scaffolds, in particular, the indeno[1,2-\textit{b}]indole system, has received extraordinary importance in the area of biological and pharmacologically active agents during the past decades.\textsuperscript{99} For example, 5,10-dihydroindeno[1,2-\textit{b}]indole is a key intermediate for the synthesis of the BARAC-Fluor reagent, used for cell labelling,\textsuperscript{100} compounds 6, 7 and 8 act as potential topoisomerase II–inhibiting anticancer agents\textsuperscript{101} and compounds 9 and 10 show high anti-cancer\textsuperscript{102} and
effective antioxidant activities, as well as radical scavenging activities (Figure III.2).\textsuperscript{[103]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure_iii_2.png}
\caption{Figure III.2}
\end{figure}

\textbf{III.2 BACKGROUND:}

Due to their interesting structural features and wide range of biological activities, there are few reports on the synthesis of fused tricyclic indoles.\textsuperscript{[104]} Notably, along with palladium catalyzed intramolecular Heck reactions and radical cyclizations, acid mediated domino strategies were employed to achieve indole based fused tetracyclic systems.\textsuperscript{[105]}

The research group of Gevorgyan reported the palladium catalyzed intramolecular annulations of N-substituted benzoylindoles 11 to the corresponding fused heterocyclic system 12. The reaction triggered a five membered ring formation, only in presence of triethylamine as base (Scheme III.1).\textsuperscript{[106]}
Larock and Campo developed cyclocarbonyl insertion followed by cyclization, using which they synthesized the fused tetracyclic ketone 14 from corresponding haloindole biaryl 13 (Scheme III.2).\cite{107}

Wu and his co-workers established the synthesis of fused indole tetracyclics 16 by an intramolecular Heck reaction of N-(2-halo)-benzoyl indoles 15 (Scheme III.3).\cite{108}

Guchhait and Kashyap disclosed an efficient two-step process involving 3-acylation of N-methyl indole 17 with 2-bromobenzoylchloride 18 followed by palladium catalyzed intramolecular annulation of 19, leading to the fused indole tetracyclic ketone 12 (Scheme III.4).\cite{109}
Similarly, the research group of Wang illustrated the synthesis of fused tetracyclic bis-indole alkaloids 22 in two steps from N-methyl indole 17 and bromo aldehydes 20 by a palladium catalyzed intramolecular Heck reaction of 21 as a key step (Scheme III.5).\textsuperscript{110}

Harrowven’s research group disclosed radical cyclization reactions on the derivatives of indoles, which led to novel five-membered fused tetracyclics 24 from the acyclic indole iodoarene derivative 23 and six-membered fused tetracyclics 26 from 25 (Scheme III.6).\textsuperscript{111}
Bennasar and his co-workers developed a new selenium based free radical cyclization, which lead to the fused tetracylic 28 from the precursor 27 (Scheme III.7). \[112\]

![Scheme III.7](image)

Direct Fischer indolization of indanones 29 with phenyl hydrazines furnished indenoindole fused tetracyclcs 30 (Scheme III.8). \[113\]

![Scheme III.8](image)

The research group of Tu reported a novel a three component domino method for the synthesis of novel tetracyclic systems 33 and 34 from ninhydrin 31 and enone 32 precursors (Scheme III.9). \[18a\]

![Scheme III.9](image)
Hamada et al disclosed an expedient method for the synthesis of 36 using an acid promoted domino cyclization of indole based enol system 36 via a dual C–C bond formation\cite{18b} (Scheme III.10).

Very recently, we developed superacid mediated dual C–C bond formation, for the efficient synthesis of indanones 39 by employing a reaction between simple ethyl cinnamates 37 and an external arene 38 (Scheme III.11).\cite{114}

**III.3 RESULTS AND DISCUSSION:**

With this background, the formation of novel tetracyclic fused systems was planned using a sequential domino one-pot process. Since both Friedel-Crafts and Fischer-indole reactions are feasible under acidic conditions, superacid (triflic acid) mediated Friedel-Crafts alkylation and acylation followed by Fischer-indole sequence was planned (Scheme III.12).
To the best of our knowledge, there have been no reports for Fischer-indole synthesis as a key step in either one-pot or sequential one-pot on the carbonyls that were generated in-situ.

The synthetic study began by choosing readily available simple ethyl cinnamate 37a as a model. Ethyl cinnamate 37a was treated under different acidic reaction conditions and the results are as summarized in Table III.1. Initially, the reaction of 37a with benzene 38a in the presence of triflic acid (TfOH) in hot DCE for 24 h, (i.e., initial formation of indanone 39a followed by in-situ Fischer indole synthesis with phenylhydrazine), furnished the tetracyclic cyclic system 40a, albeit in very poor yield (entry 1, Table III.1). However, the reaction was not clean with Lewis acids such as FeCl₃ and AlCl₃ (entries 2 to 4, Table III.1), where, neither recovery of starting material 37a nor the product 40a product were observed. In a similar fashion, addition of different Brønsted acids or Lewis acids and solvents after the formation of indanone 39a, in order to promote the subsequent Fischer-indole synthesis, was also found unproductive (entries 5 to 10, Table III.1). As most of the Fischer-indole syntheses were successful in the presence of protic solvents, addition of protic solvent EtOH as the second solvent at Fischer-indole stage, improved the yield to 22% along with the recovery of indanone 39a (entry 11, Table III.1). Interestingly, the reaction was promoted by the additional amount of TfOH (3 equiv) along with EtOH in the Fischer indole stage by improvement in the yield, although, the intermediate product 39a still prevailed and was recovered (entry 12, Table III.1). Further increase in the amount of triflic acid from 3 to 6 equiv, furnished the tetracyclic product 40a in the best yield 74% (entry 13, Table III.1). The requirement of excess TfOH is justified based on the fact that the
Table III.1: Optimization conditions for the formation of 40a.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indanone 39a formation</th>
<th>Subsequent tetracyclic fused system 40a formation by Fischer-indole synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acid (equiv)</td>
<td>Solvent</td>
</tr>
<tr>
<td>1a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>2a</td>
<td>FeCl₃ (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>3b</td>
<td>AlCl₃ (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>4c</td>
<td>-</td>
<td>TFA</td>
</tr>
<tr>
<td>5a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>6a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>7a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>8a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>9a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>10a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>11a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>12a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
<tr>
<td>13a</td>
<td>TfOH (3)</td>
<td>DCE</td>
</tr>
</tbody>
</table>

a Proceeded for the sequential one-pot formation of the tetracyclic fused systems based on the complete conversion of cinnamate by TLC. b Reaction was not clean by TLC. c No conversion of ethyl cinnamate. d Isolated yields of chromatographically pure product (40a). e Reaction was not clean by TLC. f No progress for Fischer-indole synthesis.
protic solvent EtOH and phenylhydrazine hydrochloride are good proton acceptors and hence, might reduce the acidity of triflic acid. Therefore, the conditions

Figure III.3.1: $^1$H NMR (400 MHz) spectrum of 40a in CDCl$_3$

Figure III.3.2: $^{13}$C NMR (100 MHz) spectrum of 40a in CDCl$_3$
of entry 13 in Table III.1 turned out to be the best conditions and were applied to the other cinnamates 37 in order to check the scope and feasibility of the method.

The formation and structure of the tetracyclic compound 40a was evident from spectral data. The absence of the absorption band due to carbonyl stretching of aldehyde group and the presence of the broad absorption band at 3334 cm$^{-1}$ due to N–H stretching in the IR spectrum indicated the formation of 40a. It was further proved from the $^1$H-NMR spectrum (Figure III.3.1), by the presence of a broad singlet at δ 8.31 due to N–H proton, a doublet of doublet at 7.40 due to two aromatic protons, a doublet of doublet at δ 7.00 for one aromatic proton, and one singlet at δ 4.93 ppm for one aliphatic proton elucidated the structure of the tetracyclic compound 40a. In addition, in 18 lines of $^{13}$C-NMR spectrum (Figure III.3.2), the presence of six quaternary carbon resonances at δ 152.7, 142.8, 140.7, 140.5, 134.2 and 124.3 due to six aromatic carbons and 11 aromatic methine carbons at δ 128.6, 127.9, 127.0, 126.7, 125.5, 125.4, 121.9, 120.3, 119.0, 117.4 and 112.1 resulting from 13 aromatic protons and one aliphatic methane at 48.7 ppm confirmed the structure of 40a.

With the optimized reaction conditions in hand (entry 13, Table III.1), we further investigated the scope and limitations of the method using different ethyl cinnamates 37a–37i, and the results are summarized in the Table III.2. Delightfully, this method proved to be efficient and amenable for a broad range of substrates with various substituents on the aromatic rings and furnished the corresponding fused tetracyclic products 40a–40o containing a tertiary carbon atom at the 10$^{th}$-position, in moderate to very good yields (Table III.2). Moreover, this protocol was also successfully applied to products 40p–40t possessing a quaternary carbon center at the 10$^{th}$-position (Table III.2). The method was found applicable to different aryl hydrazines and furnished the corresponding tetracyclic products 40c and 40l as shown in Table III.2. The regiochemistry of compound 40t can be justified on the less sterically crowded methoxy group over the bromo substituent of 38e that facilitates the initial Friedel-Crafts alkylation ortho to the methoxy group, which is
further confirmed by the 2D-NMR analysis. It is worth mentioning that among the two aromatic moieties, one from cinnamate 37 and the other from external arene 38, for the initial indanone 39 formation, an aromatic ring that was relatively more rich in electrons selectively participated in the formation of intramolecular acylation (intramolecular condensation), after the Friedel-Crafts alkylation (Michael addition type).

Other than spectroscopic evidence that confirmed the structure of compounds 40, their complete structures were unambiguously confirmed by single crystal X-ray diffraction analysis of 40m (Figure III.4).
Table III.2: Synthesis of fused tetracyclic systems 40a–40l.\textsuperscript{a}

Yields in the parenthesis are the isolated yields of chromatographically pure products.

\textsuperscript{a} Yields in the parenthesis are the isolated yields of chromatographically pure products.
III.4. CONCLUSIONS:

In summary, an efficient sequential domino one-pot method was developed for the synthesis of novel fused tetracyclic indole systems via Friedel-Crafts alkylation and acylation followed by Fischer-indole reaction. These ubiquitous fused tetracyclic systems are found to be present in various biologically active alkaloid natural products. Additionally, such systems represent many biologically active scaffolds. Overall, this protocol illustrates the potential of sequential domino one-pot reactions in the field of organic chemistry.

![Chemical structure](image)

III.5 EXPERIMENTAL SECTION

General:

IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. $^1$H-NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in CDCl$_3$; chemical shifts ($\delta$ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) ($\delta_H =0.00$ ppm) or CHCl$_3$ ($\delta_H = 7.25$ ppm). $^{13}$C-NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at RT in CDCl$_3$; chemical shifts ($\delta$ ppm) are reported relative to CHCl$_3$ [\(\delta_C = 77.00\) ppm (central line of triplet)]. In the $^{13}$C-NMR, the nature of carbons (C, CH, CH$_2$ and CH$_3$) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH$_2$) and q = quartet (for CH$_3$). In the $^1$H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, sept = septet, dd = doublet of doublet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by
\(^1\)H, \(^{13}\)C carbon proton decoupled (CPD) and distortionless enhancement polarization transfer (DEPT) spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF electron spray ionization (ESI) mode and atmospheric pressure chemical ionization (APCI) modes. All small scale dry reactions were carried out using Schlenk tubes under inert atmosphere. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Reactions were generally run under argon or a nitrogen atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C was used. Dichloroethane (DCE) was dried over CaH\(_2\) and absolute ethanol was purchased from local sources, used as received. Trifluoromethanesulfonic acid (triflic acid) was purchased from Spectrochem Pvt. Ltd. And used as received. Acme’s silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

Ethyl cinnamate 37a is commercially available, and other ethyl cinnamates 37b,\(^{[115]}\) 37c,\(^{[116]}\) 37d,\(^{[117]}\) 37e,\(^{[118]}\) 37f,\(^{[119]}\) 37g,\(^{[120]}\) 37h,\(^{[121]}\) and 37i\(^{[122]}\) are known in the literature.

![Chemical Structures](image-url)
Compound 40a\textsuperscript{[123]} is also known in the literature.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{40a.png}
\caption{Structure of compound 40a.}
\end{figure}

X-ray crystal structure data for 10-(4-bromophenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-b]indole (40m): CCDC 990792

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{40m.png}
\caption{Structure of compound 40m.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Operator} & K. Ravikumar \\
\textbf{Instrument} & Oxford SuperNova \\
\hline
Empirical formula & C\textsubscript{23}H\textsubscript{18}BrN \\
Formula weight & 388.29 \\
Temperature/K & 566(2) \\
Crystal system & monoclinic \\
Space group & P2\textsubscript{1}/c \\
a/Å & 15.3751(5) \\
b/Å & 5.2210(2) \\
c/Å & 22.8112(7) \\
\hline
\end{tabular}
\caption{Crystallographic data for compound 40m.}
\end{table}
α/°  90.00
β/°  103.036(3)
γ/°  90.00

Volume/Å³  1783.95(11)
Z  4

ρ_{calc} mg/mm³  1.446
m/mm⁻¹  3.151
F(000)  792.0

Crystal size/mm³  0.19 × 0.17 × 0.15

2θ range for data collection  5.9 to 141.3°

Index ranges  
-18 ≤ h ≤ 11, -6 ≤ k ≤ 3, -26 ≤ l ≤ 27

Reflections collected  6233
Independent reflections  3327[R(int) = 0.0228]

Data/restraints/parameters  3327/0/228

Goodness-of-fit on F²  1.257

Final R indexes [I≥2σ(I)]  R₁ = 0.0499, wR₂ = 0.1642

Final R indexes [all data]  R₁ = 0.0622, wR₂ = 0.1824

Largest diff. peak/hole / e Å⁻³  0.36/-0.88

**General Procedure for the Preparation of 10-Phenyl-5,10-dihydroindeno[1,2-b]-indoles (GP-1):**

In an oven dried Schlenk tube, were added cinnamate 37 (88.0–134.0 mg, 0.50 mmol), arene 38 [468.0–636 mg, 6.0 mmol (139.4 mg, 0.75 mmol in case of 3-bromoanisole)] and dichloroethane (1.5 mL) followed by triflic acid (0.13 mL, 1.5 mmol) at room temperature under nitrogen atmosphere and allowed the reaction mixture to stir at 80 °C for 24 h. Progress of the indanone 39 formation was
monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added aryl hydrazine hydrochloride (144.6–178.0 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 6.0 mmol) under nitrogen atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 12 h and monitored by TLC. Then, the mixture was quenched by the addition of aqueous NaHCO₃ solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the tetracyclic system 40 (102.8–159.7 mg, 51–89%) as viscous liquid/solid.

10-(4-Chlorophenyl)-5,10-dihydroindeno[1,2-b]indole (40b):

GP-1 was carried out with cinnamate 37b (105.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39b formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40b (113.4 mg, 72%) as a brown solid, was recrystallized the solid with dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), Rf(37b)=0.51, Rf(40b)=0.37, UV detection].

M.p.: 180–184 °C.

IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\max} \) = 3402, 2923, 1605, 1487, 1440, 1385, 1303, 1088, 1014, 814, 738 cm⁻¹.
\[^{1}\text{H-NMR (CDCl}_3, 400 \text{ MHz)}: \delta=8.35 \text{ (br. s, 1H, NH), 7.46 (dd, 2H, } J=7.3 \text{ and 7.3 Hz, Ar-H), 7.33 (dd, 2H, } J=7.8 \text{ and 7.8 Hz, Ar-H), 7.31 (d, 1H, } J=7.8 \text{ Hz, Ar-H), 7.24 (d, 2H, } J=8.8 \text{ Hz, Ar-H), 7.22–7.15 (m, 2H, Ar-H), 7.15 (d, 2H, } J=8.8 \text{ Hz, Ar-H), 7.08 (ddd, 1H, } J=8.3, 7.8 \text{ and 1.0 Hz, Ar-H), 4.94 (s, 1H, CH) ppm.}
\]

\[^{13}\text{C-NMR (CDCl}_3, 100 \text{ MHz)}: \delta=152.3 \text{ (s, Ar-C), 142.9 (s, Ar-C), 140.7 (s, Ar-C), 139.2 (s, 2C, 2 \times Ar-C), 134.1 (s, Ar-C), 132.4 (s, Ar-C), 129.3 (d, 2C, Ar-CH), 128.8 (d, 2C, Ar-CH), 127.2 (d, Ar-CH), 125.6 (d, Ar-CH), 125.3 (d, Ar-CH), 124.1 (s, Ar-C), 122.0 (d, Ar-CH), 120.5 (d, Ar-CH), 118.8 (d, Ar-CH), 117.5 (d, Ar-CH), 112.2 (d, Ar-CH), 47.9 (d, CH) ppm.}
\]

**HR-MS (ESI\(^+\)):** m/z calculated for \([\text{C}_{21}\text{H}_{14}\text{ClNNa}]+=[\text{M+Na}]^+: 338.0707; \) found 338.0708.

![Chemical Structure](image)

**8-Chloro-10-phenyl-5,10-dihydroindeno[1,2-b]indole (40c):**

\(\text{GP-1} \text{ was carried out with cinnamate } 37a \text{ (88.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichloroethane (1.5 mL) at 80 } ^\circ\text{C for 24 h for the indanone } 39c \text{ formation, and then with para-chlorophenylhydrazine hydrochloride (178.0 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 } ^\circ\text{C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system } 40c \text{ (107.1 mg, 68%) as a pale brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), } R_f(37a)=0.50, R_f(40c)=0.36, \text{ UV detection].}
\]

**M.p.:** 198–200 °C.
IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{\max}=3343, 2925, 1599, 1491, 1449, 1292, 1069, 937, 761, 701$ cm$^{-1}$.

$^1$H-NMR [(CDCl$_3$ + DMSO-D$_6$), 400 MHz]: $\delta=10.90$ (br. s, 1H, NH), 6.90 (d, 1H, $J=7.3$ Hz, Ar-H), 6.70 (d, 1H, $J=8.8$ Hz, Ar-H), 6.65–6.38 (m, 9H, Ar-H), 6.29 (dd, 1H, $J=8.8$ and 2.0 Hz, Ar-H), 4.24 (s, 1H, CH) ppm.

$^{13}$C-NMR [(CDCl$_3$ + DMSO-D$_6$), 100 MHz]: $\delta=150.9$ (s, Ar-C), 143.4 (s, Ar-C), 139.2 (s, Ar-C), 137.9 (s, Ar-C), 132.6 (s, Ar-C), 127.1 (d, 2C, Ar-CH), 126.1 (d, 2C, Ar-CH), 125.5 (d, Ar-CH), 125.2 (d, Ar-CH), 124.1 (d, Ar-CH), 123.7 (d, Ar-CH), 123.2 (s, Ar-C), 123.0 (s, Ar-C), 121.9 (s, Ar-C), 119.3 (d, Ar-CH), 116.8 (d, Ar-CH), 115.8 (d, Ar-CH), 112.1 (d, Ar-CH), 46.5 (d, CH) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{21}$H$_{14}$ClNNa]$^+=[M+Na]$^+: 338.0707; found 338.0691.

10-(4-Bromophenyl)-5,10-dihydroindeno[1,2-b]indole (40d):

GP-1 was carried out with cinnamate 37d (127.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39d formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40d (126.1 mg, 70%) as a brown semi-solid. [TLC control (petroleum ether/ethyl acetate 95:5), $R_f$(37d)=0.53, $R_f$(40d)=0.38, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{\max}=3410, 3056, 1611, 1485, 1444, 1386, 1305, 1069, 1011, 740$ cm$^{-1}$.
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta=8.41$ (br. s, 1H, NH), 7.46 (dd, 2H, $J=8.3$ and 7.8 Hz, Ar-H), 7.38 (d, 2H, $J=8.3$ Hz, Ar-H), 7.35–7.28 (m, 3H, Ar-H), 7.13–7.22 (m, 2H, Ar-H), 7.09 (d, 2H, $J=8.3$ Hz, Ar-H), 7.10–7.04 (m, 1H, Ar-H), 4.92 (s, 1H, CH) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta=152.1$ (s, Ar-C), 142.9 (s, Ar-C), 140.7 (s, Ar-C), 139.7 (s, 2C, 2 × Ar-C), 134.1 (s, Ar-C), 131.7 (d, 2C, Ar-CH), 129.6 (d, 2C, Ar-CH), 127.2 (d, Ar-CH), 125.6 (d, Ar-CH), 125.3 (d, Ar-CH), 125.2 (s, Ar-C), 124.1 (s, Ar-C), 122.0 (d, Ar-CH), 120.5 (d, Ar-CH), 118.8 (d, Ar-CH), 117.5 (d, Ar-CH), 112.2 (d, Ar-CH), 48.0 (d, CH) ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{21}$H$_{15}$BrN]$^+=[M+H]$: 362.0382; found 362.0360.

3-Methyl-10-phenyl-5,10-dihydroindeno[1,2-b]indole (40e):

GP-1 was carried out with cinnamate 37a (88.0 mg, 0.50 mmol), toluene (552.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39e formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40e (90.1 mg, 61%) as a brown semi-solid. [TLC control (petroleum ether/ethyl acetate 95:5), $R_f$(37a)=0.50, $R_f$(40e)=0.36, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}=3409, 2920, 1599, 1491, 1451, 1248, 907, 730$ cm$^{-1}$. 

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$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta=8.27$ (br. s, 1H, NH), 7.33 (d, 1H, $J=7.8$ Hz, Ar-H), 7.26 (d, 2H, $J=7.8$ Hz, Ar-H), 7.20–6.90 (m, 8H, Ar-H), 6.88 (d, 1H, $J=7.3$ Hz, Ar-H), 4.86 (s, 1H, CH), 2.31 (s, 3H, Ar-CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta=$149.9 (s, Ar-C), 142.8 (s, Ar-C), 140.9 (s, Ar-C), 136.7 (s, Ar-C), 134.3 (s, Ar-C), 129.3 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.5 (s, Ar-C), 127.9 (d, 2C, Ar-CH), 126.6 (d, Ar-CH), 126.2 (d, Ar-CH), 125.0 (d, Ar-CH), 124.4 (s, Ar-C), 121.7 (d, Ar-CH), 120.3 (d, Ar-CH), 118.9 (d, Ar-CH), 118.3 (d, Ar-CH), 112.1 (d, Ar-CH), 48.3 (d, CH), 21.5 (q, Ar-CH$_3$) ppm.

HR-MS (ESI): m/z calculated for [C$_{22}$H$_{17}$KN]$^+$=[M+K]$^+$: 334.0993; found 334.0986.

1,3-Dimethyl-10-phenyl-5,10-dihydroindenophenyl-1,2-b]indole (40f):

GP-1 was carried out with cinnamate 37a (88.0 mg, 0.50 mmol), $m$-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39f formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40f (117.6 mg, 76%) as a brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), $R_f$(37a)=0.50, $R_f$(40f)=0.36, UV detection].

M.p.: 194–198 °C.

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}=$3387, 2921, 1600, 1493, 1450, 1304, 1253, 907, 730 cm$^{-1}$.
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta=8.28$ (br. s, 1H, NH), 7.38 (d, 1H, $J=8.3$ Hz, Ar-H), 7.34 (d, 1H, $J=7.8$ Hz, Ar-H), 7.24–7.13 (m, 6H, Ar-H), 7.10 (ddd, 1H, $J=8.3$, 7.8 and 1.0 Hz, Ar-H), 7.01 (ddd, 1H, $J=7.8$, 7.8 and 1.0 Hz, Ar-H), 6.81 (s, 1H, Ar-H), 4.92 (s, 1H, CH), 2.42 (s, 3H, Ar-CH$_3$), 2.04 (s, 3H, Ar-CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta=147.5$ (s, Ar-C), 142.0 (s, Ar-C), 140.5 (s, Ar-C), 140.4 (s, Ar-C), 137.2 (s, Ar-C), 135.1 (s, Ar-C), 135.0 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 128.2 (d, Ar-CH), 127.9 (d, 2C, Ar-CH), 127.7 (s, Ar-C), 126.3 (d, Ar-CH), 124.1 (s, Ar-C), 121.6 (d, Ar-CH), 120.2 (d, Ar-CH), 118.4 (d, Ar-CH), 116.0 (d, Ar-CH), 111.9 (d, Ar-CH), 48.2 (d, CH), 21.4 (q, Ar-CH$_3$), 18.7 (q, Ar-CH$_3$) ppm.

HR-MS (ESI‒): m/z calculated for [C$_{23}$H$_{23}$N$_2$]$^+=[M+NH$_4$]$^+$: 327.1856; found 327.1841.

10-(4-Chlorophenyl)-1,3-dimethyl-5,10-dihydroindeno[1,2-b]indole (40g):

GP-1 was carried out with cinnamate $37b$ (105.0 mg, 0.50 mmol), m-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone $39g$ formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system $40g$ (104.8 mg, 61%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), $R_f(37b)=0.51$, $R_f(40g)=0.36$, UV detection].

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{max}=3406, 2921, 1615, 1488, 1454, 1305, 1014, 845, 742$ cm$^{-1}$. 

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$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$=8.28 (br. s, 1H, NH), 7.39 (d, 1H, $J$=7.8 Hz, Ar-H), 7.30 (d, 1H, $J$=7.8 Hz, Ar-H), 7.22–7.14 (m, 3H, Ar-H), 7.11 (ddd, 1H, $J$=7.8, 7.8 and 1.0 Hz, Ar-H), 7.07 (d, 2H, $J$=8.3 Hz, Ar-H), 7.01 (ddd, 1H, $J$=7.8, 7.3 and 1.0 Hz, Ar-H), 6.80 (s, 1H, Ar-H), 4.89 (s, 1H, CH), 2.41 (s, 3H, Ar-CH$_3$), 2.03 (s, 3H, Ar-CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$=147.1 (s, Ar-C), 142.0 (s, Ar-C), 140.5 (s, Ar-C), 139.2 (s, Ar-C), 137.5 (s, Ar-C), 135.0 (s, Ar-C), 134.9 (s, Ar-C), 131.9 (s, Ar-C), 129.3 (d, 2C, Ar-CH), 128.7 (d, 2C, Ar-CH), 128.3 (d, Ar-CH), 127.3 (s, Ar-C), 124.0 (s, Ar-C), 121.8 (d, Ar-CH), 120.3 (d, Ar-CH), 118.3 (d, Ar-CH), 116.1 (d, Ar-CH), 112.0 (d, Ar-CH), 47.4 (d, CH), 21.4 (q, Ar-CH$_3$), 18.7 (q, Ar-CH$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{23}$H$_{19}$ClN]$^+$=[M+H]$^+$: 344.1201; found 344.1197.

10-(4-Bromophenyl)-1,3-dimethyl-5,10-dihydroindeno[1,2-b]indole (40h):

GP-1 was carried out with cinnamate 37d (127.0 mg, 0.50 mmol), m-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39h formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40h (106.8 mg, 55%) as a brown semi-solid. [TLC control (petroleum ether/ethyl acetate 95:5), $R_f$(37d)=0.53, $R_f$(40h)=0.37, UV detection].
IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \(\nu_{\text{max}}=3356, 2921, 1588, 1484, 1451, 1262, 1246, 1070, 1010, 739\) cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta=8.27\) (br. s, 1H, NH), 7.39 (d, 1H, \(J=8.3\) Hz, Ar-H), 7.33 (d, 2H, \(J=8.3\) Hz, Ar-H), 7.32 (d, 1H, \(J=8.3\) Hz, Ar-H), 7.17 (s, 1H, Ar-H), 7.12 (ddd, 1H, \(J=8.3, 7.8\) and 1.0 Hz, Ar-H), 7.03 (d, 2H, \(J=8.3\) Hz, Ar-H), 7.02 (ddd, 1H, \(J=8.3, 7.8\) and 1.0 Hz, Ar-H), 6.81 (s, 1H, Ar-H), 4.87 (s, 1H, CH), 2.41 (s, 3H, Ar-CH\(_3\)), 2.03 (s, 3H, Ar-CH\(_3\)) ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta=147.0\) (s, Ar-C), 142.0 (s, Ar-C), 140.5 (s, Ar-C), 139.7 (s, Ar-C), 137.5 (s, Ar-C), 135.0 (s, Ar-C), 134.9 (s, Ar-C), 131.6 (d, 2C, Ar-CH), 129.7 (d, 2C, Ar-CH), 128.3 (d, Ar-CH), 127.1 (s, Ar-C), 123.9 (s, Ar-C), 121.8 (d, Ar-CH), 120.3 (d, Ar-CH), 119.9 (s, Ar-C), 118.3 (d, Ar-CH), 116.1 (d, Ar-CH), 112.0 (d, Ar-CH), 47.5 (d, CH), 21.4 (q, Ar-CH\(_3\)), 18.7 (q, Ar-CH\(_3\)) ppm.

HR-MS (ESI\(^-\)): m/z calculated for [C\(_{23}\)H\(_{17}\)BrN\(^-\)]\(^-\)=[M−H\(^-\)]: 386.0550; found 386.0558.

1,4-Dimethyl-10-phenyl-5,10-dihydroindeno[1,2-b]indole (40i):

GP-1 was carried out with cinnamate 37a (88.0 mg, 0.50 mmol), \(p\)-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39i formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40i (129.9 mg, 84%) as a pale yellow solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), \(R_f(37a)=0.50, R_f(40i)=0.35, \) UV detection].
M. p.: 198–200 °C.

IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 3445, 3023, 1598, 1478, 1444, 1296, 1243, 1078, 1029, 907, 733 \text{ cm}^{-1} \).

\(^1\)H-NMR (CDCl₃, 400 MHz): \( \delta = 8.33 \) (br. s, 1H, NH), 7.42 (d, 1H, \( J = 8.3 \) Hz, Ar-H), 7.36 (d, 1H, \( J = 7.8 \) Hz, Ar-H), 7.25–7.09 (m, 6H, Ar-H), 7.07 (d, 1H, \( J = 7.8 \) Hz, Ar-H), 7.02 (ddd, 1H, \( J = 8.3, 7.8 \) and 1.0 Hz, Ar-H), 6.89 (d, 1H, \( J = 7.8 \) Hz, Ar-H), 4.93 (s, 1H, CH), 2.67 (s, 3H, Ar-CH₃), 2.04 (s, 3H, Ar-CH₃) ppm.

\(^{13}\)C-NMR (CDCl₃, 100 MHz): \( \delta = 150.1 \) (s, Ar-C), 142.4 (s, Ar-C), 140.8 (s, Ar-C), 140.4 (s, Ar-C), 134.2 (s, Ar-C), 132.8 (s, Ar-C), 128.9 (d, Ar-CH), 128.5 (d, 2C, Ar-CH), 127.9 (d, 2C, Ar-CH), 127.5 (d, Ar-CH), 127.1 (s, Ar-C), 126.3 (d, Ar-CH), 125.5 (s, Ar-C), 123.9 (s, Ar-C), 121.5 (d, Ar-CH), 120.2 (d, Ar-CH), 118.4 (d, Ar-CH), 111.9 (d, Ar-CH), 48.4 (d, CH), 19.1 (q, Ar-CH₃), 18.5 (q, Ar-CH₃) ppm.

HR-MS (ESI⁻): m/z calculated for \([\text{C}_{23}\text{H}_{19}\text{NNa}]^{+} = [\text{M+Na}]^{+} \): 332.1410; found 332.1404.

10-(4-Chlorophenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-b]indole (40j):

GP-1 was carried out with cinnamate 37b (105.0 mg, 0.50 mmol), \( p \)-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39j formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40j (123.7 mg, 72%) as a brown semi-solid. [TLC control (petroleum ether/ethyl acetate 95:5), \( R_f(37b) = 0.51 \), \( R_f(40j) = 0.36 \), UV detection].
IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \(\nu_{\text{max}}\) = 3454, 2922, 1592, 1488, 1444, 1298, 1087, 1014, 803, 741 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta = 8.33\) (br. s, 1H, NH), 7.43 (d, 1H, \(J = 7.8\) Hz, Ar-H), 7.32 (d, 1H, \(J = 7.8\) Hz, Ar-H), 7.18 (d, 2H, \(J = 8.3\) Hz, Ar-H), 7.12 (dd, 1H, \(J = 7.8\) and 7.3 Hz, Ar-H), 7.07 (d, 2H, \(J = 8.3\) Hz, Ar-H), 7.06 (d, 1H, \(J = 7.8\) Hz, Ar-H), 7.03 (dd, 1H, \(J = 7.8\) and 7.3 Hz, Ar-H), 6.88 (d, 1H, \(J = 7.8\) Hz, Ar-H), 4.89 (s, 1H, CH), 2.66 (s, 3H, Ar-CH\(_3\)), 2.03 (s, 3H, Ar-CH\(_3\)) ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta = 149.6\) (s, Ar-C), 142.4 (s, Ar-C), 140.8 (s, Ar-C), 139.1 (s, Ar-C), 134.1 (s, Ar-C), 132.7 (s, Ar-C), 131.9 (s, Ar-C), 129.3 (d, 2C, Ar-CH), 129.1 (d, Ar-CH), 128.7 (d, 2C, Ar-CH), 127.6 (d, Ar-CH), 126.6 (s, Ar-C), 125.7 (s, Ar-C), 123.7 (s, Ar-C), 121.6 (d, Ar-CH), 120.4 (d, Ar-CH), 118.2 (d, Ar-CH), 112.0 (d, Ar-CH), 47.6 (d, CH), 19.1 (q, Ar-CH\(_3\)), 18.5 (q, Ar-CH\(_3\)) ppm.

HR-MS (ESI\(^+\)): m/z calculated for \([C_{23}H_{19}ClN]^+ = [M+H]^+\): 344.1201; found 344.1193.

10-(2-Chlorophenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-b]indole (40k):

GP-1 was carried out with cinnamate 37c (105.0 mg, 0.50 mmol), \(p\)-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichloroethane (1.5 mL) at 80 °C for 24 h for the indanone 39k formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40k (127.2 mg, 74%) as a pale brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), \(R_f(37c) = 0.51\), \(R_f(40k) = 0.36\), UV detection].
IR (neat; MIR-ATR, 4000–600 cm⁻¹): \( \nu_{\text{max}} = 3375, 2923, 1593, 1489, 1443, 1299, 1151, 1130, 1038, 820, 746 \text{ cm}^{-1} \).

\(^1\)H-NMR (CDCl₃, 400 MHz): \( \delta = 8.30 \) (br. s, 1H, NH), 7.51 (d, 1H, \( J = 7.8 \) Hz, Ar-H), 7.50 (dd, 1H, \( J = 7.8 \) and 1.0 Hz, Ar-H), 7.42 (d, 1H, \( J = 7.8 \) Hz, Ar-H), 7.14 (ddd, 1H, \( J = 8.3, 7.8 \) and 1.0 Hz, Ar-H), 7.12–7.02 (m, 3H, Ar-H), 6.92 (d, 1H, \( J = 8.3 \) Hz, Ar-H), 6.89 (d, 1H, \( J = 8.3 \) Hz, Ar-H), 6.44 (dd, 1H, \( J = 7.8 \) and 1.5 Hz, Ar-H), 5.53 (s, 1H, CH), 2.67 (s, 3H, Ar-CH₃), 2.00 (s, 3H, Ar-CH₃) ppm.

\(^{13}\)C-NMR (CDCl₃, 100 MHz): \( \delta = 150.1 \) (s, Ar-C), 142.6 (s, Ar-C), 140.7 (s, Ar-C), 138.0 (s, Ar-C), 134.3 (s, Ar-C), 134.2 (s, Ar-C), 134.2 (s, Ar-C), 129.3 (d, Ar-CH), 129.0 (d, Ar-CH), 128.1 (d, Ar-CH), 127.6 (d, Ar-CH), 127.5 (d, Ar-CH), 127.2 (d, Ar-CH), 126.7 (s, Ar-C), 125.6 (s, Ar-C), 123.6 (s, Ar-C), 121.6 (d, Ar-CH), 120.4 (d, Ar-CH), 119.0 (d, Ar-CH), 111.8 (d, Ar-CH), 43.8 (d, CH), 19.1 (q, Ar-CH₃), 18.0 (q, Ar-CH₃) ppm.

HR-MS (ESI⁺): m/z calculated for \([C_{23}H_{18}ClN]^+ = [M]^+\): 343.1122; found 343.1129.

8-Chloro-1,4-dimethyl-10-phenyl-5,10-dihydroindeno[1,2-b]indole (40l):

GP-1 was carried out with cinnamate 37a (88.0 mg, 0.50 mmol), \( p \)-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39l formation, and then with \( p \)-chlorophenyl hydrazine hydrochloride (178.0 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40l (130.6 mg,
76%) as a pale brown solid, which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 95:5), $R_f(37a)=0.50$, $R_f(40l)=0.36$, UV detection].

**M.p.:** 224–226 °C.

**IR (neat; MIR-ATR, 4000–600 cm$^{-1}$):** $\nu_{max}$=3444, 2922, 1600, 1452, 1289, 1057, 797 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$=8.31 (br. s, 1H, NH), 7.30 (d, 1H, $J$=8.8 Hz, Ar-H), 7.28 (d, 1H, $J$=1.9 Hz, Ar-H), 7.21 (d, 2H, $J$=7.8 Hz, Ar-H), 7.17 (t, 1H, $J$=7.3 Hz, Ar-H), 7.13–7.00 (m, 4H, Ar-H), 6.90 (d, 1H, $J$=7.8 Hz, Ar-H), 4.85 (s, 1H, CH), 2.64 (s, 3H, Ar-CH$_3$), 2.01 (s, 3H, Ar-CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$=150.1 (s, Ar-C), 143.8 (s, Ar-C), 139.9 (s, Ar-C), 139.0 (s, Ar-C), 133.6 (s, Ar-C), 132.9 (s, Ar-C), 129.0 (d, Ar-CH), 128.7 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.8 (d, 2C, Ar-CH), 126.5 (s, Ar-C), 126.4 (s, Ar-C), 125.9 (s, Ar-C), 125.8 (s, Ar-C), 124.8 (s, Ar-C), 121.5 (d, Ar-CH), 117.7 (d, Ar-CH), 112.7 (d, Ar-CH), 48.2 (d, CH), 19.1 (q, Ar-CH$_3$), 18.4 (q, Ar-CH$_3$) ppm.

**HR-MS (ESI$^+$):** m/z calculated for [C$_{23}$H$_{19}$ClN]$^+$=[M+H]$^+$: 344.1201; found 344.1199.

**10-(4-Bromophenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-b]indole (40m):**

GP-1 was carried out with cinnamate 37d (127.0 mg, 0.50 mmol), $p$-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39m formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the
crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40m (172.0 mg, 89%) as a brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), $R_f(37d)=0.53$, $R_f(40m)=0.37$, UV detection].

M.p.: 228–230 °C

IR (neat; MIR-ATR, 4000–600 cm$^{-1}$): $\nu_{\text{max}}$=3443, 2918, 1591, 1485, 1444, 1298, 1070, 1010, 908, 803, 731 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$=8.32 (br. s, 1H, NH), 7.43 (d, 1H, $J$=7.8 Hz, Ar-H), 7.35–7.28 (m, 1H, Ar-H), 7.33 (d, 2H, $J$=8.3 Hz, Ar-H), 7.13 (ddd, 1H, $J$=8.3, 7.3 and 1.0 Hz, Ar-H), 7.08 (d, 1H, $J$=7.8 Hz, Ar-H), 7.05 (d, 1H, $J$=7.8 Hz, Ar-H), 7.01 (d, 2H, $J$=8.3 Hz, Ar-H), 6.89 (d, 1H, $J$=7.3 Hz, Ar-H), 4.86 (s, 1H, CH), 2.65 (s, 3H, Ar-CH$_3$), 2.03 (s, 3H, Ar-CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$=149.6 (s, Ar-C), 142.4 (s, Ar-C), 140.7 (s, Ar-C), 139.7 (s, Ar-C), 134.1 (s, Ar-C), 132.7 (s, Ar-C), 131.6 (d, 2C, Ar-CH), 129.7 (d, 2C, Ar-CH), 129.1 (d, Ar-CH), 127.6 (d, Ar-CH), 126.4 (s, Ar-C), 125.7 (s, Ar-C), 123.7 (s, Ar-C), 121.6 (d, Ar-CH), 120.4 (d, Ar-CH), 119.9 (s, Ar-C), 118.2 (d, Ar-CH), 112.0 (d, Ar-CH), 47.6 (d, CH), 19.1 (q, Ar-CH$_3$), 18.5 (q, Ar-CH$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{23}$H$_{18}$BrN]$^+$=[M]$^+$: 387.0623; found 387.0605.

1,4-Dimethyl-10-(4-methylphenyl)-5,10-dihydroindeno[1,2-b]indole (40n):

GP-1 was carried out with cinnamate 37e (95.0 mg, 0.50 mmol), p-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at
80 °C for 24 h for the indanone 39n formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40n (100.2 mg, 62%) as a pale brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), Rf(37e)=0.52, Rf(40n)=0.37, UV detection].

M.p.: 204–208 °C

IR (neat; MIR-ATR, 4000–600 cm⁻¹): νmax=3440, 2917, 1589, 1510, 1479, 1443, 1298, 1244, 906, 801, 728 cm⁻¹.

¹H-NMR (CDCl₃, 400 MHz): δ=8.29 (br. s, 1H, NH), 7.42 (d, 1H, J=7.8 Hz, Ar-H), 7.42 (d, 1H, J=7.8 Hz, Ar-H), 7.39 (d, 1H, J=7.8 Hz, Ar-H), 7.13 (ddd, 1H, J=8.3, 7.8 and 1.0 Hz, Ar-H), 7.08 (d, 1H, J=7.3 Hz, Ar-H), 7.07–6.98 (m, 4H, Ar-H), 6.90 (d, 1H, J=7.8 Hz, Ar-H), 4.89 (s, 1H, CH), 2.66 (s, 3H, Ar-CH₃), 2.28 (s, 3H, Ar-CH₃), 2.06 (s, 3H, Ar-CH₃) ppm.

¹³C-NMR (CDCl₃, 100 MHz): δ=150.2 (s, Ar-C), 142.3 (s, Ar-C), 140.8 (s, Ar-C), 137.1 (s, Ar-C), 135.7 (s, Ar-C), 134.1 (s, Ar-C), 132.8 (s, Ar-C), 129.2 (d, 2C, Ar-CH), 128.8 (d, Ar-CH), 127.7 (d, 2C, Ar-CH), 127.4 (d, Ar-CH), 127.2 (s, Ar-C), 125.5 (s, Ar-C), 123.9 (s, Ar-C), 121.4 (d, Ar-CH), 120.2 (d, Ar-CH), 118.4 (d, Ar-CH), 111.9 (d, Ar-CH), 48.0 (d, CH), 21.0 (q, Ar-CH₃), 19.1 (q, Ar-CH₃), 18.5 (q, Ar-CH₃) ppm.

HR-MS (ESI⁺): m/z calculated for [C₂₄H₂₂N⁺]=M+H⁺: 324.1747; found 324.1745.

![Diagram](image-url)
10-(4-Isopropylphenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-b]indole (40o):

**GP-1** was carried out with cinnamate 37f (109.0 mg, 0.50 mmol), p-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39o formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40o (105.4 mg, 60%) as a pale orange solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), Rf(37f)=0.53, Rf(40o)=0.38, UV detection].

**M.p.:** 182–184 °C

**IR (neat; MIR-ATR, 4000–600 cm⁻¹):** \( \nu_{max} = 3379, 2959, 1602, 1485, 1454, 1298, 1245, 1053, 804, 743 \text{ cm}^{-1} \).

\(^1\text{H-NMR (CDCl}_3, 400 \text{ MHz)}: \delta = 8.29 \text{ (br. s, 1H, NH), 7.42 (d, 1H, J=8.3 Hz, Ar-H), 7.41 (d, 1H, J=7.8 Hz, Ar-H), 7.13 (dd, 1H, J=7.8 and 7.3 Hz, Ar-H), 7.09–6.96 (m, 6H, Ar-H), 6.89 (d, 1H, J=8.3 Hz, Ar-H), 4.90 (s, 1H, CH), 2.84 [sept, 1H, J=6.8 Hz, -CH(CH}_3)_2], 2.66 (s, 3H, Ar-CH}_3), 2.05 (s, 3H, Ar-CH}_3), 1.20 [d, 6H, J=6.8 Hz, -CH(CH}_3)_2] \text{ ppm}.\)

\(^{13}\text{C-NMR (CDCl}_3, 100 \text{ MHz)}: \delta = 150.2 \text{ (s, Ar-C), 146.6 (s, Ar-C), 142.3 (s, Ar-C), 140.8 (s, Ar-C), 137.3 (s, Ar-C), 134.1 (s, Ar-C), 132.8 (s, Ar-C), 128.8 (d, Ar-CH), 127.7 (d, 2C, Ar-CH), 127.4 (d, Ar-CH), 127.2 (s, Ar-C), 126.5 (d, 2C, Ar-CH), 125.4 (s, Ar-C), 123.9 (s, Ar-C), 121.4 (d, Ar-CH), 120.1 (d, Ar-CH), 118.5 (d, Ar-CH), 111.9 (d, Ar-CH), 48.0 (d, CH), 33.6 [d, -CH(CH}_3)_2], 24.0 [q, -CH(CH}_3)_2b], 23.9 [q, -CH(CH}_3)_2b], 19.1 (q, Ar-CH}_3), 18.5 (q, Ar-CH}_3) \text{ ppm}.\)

**HR-MS (ESI⁺):** m/z calculated for [C\textsubscript{26}H\textsubscript{26}N]\(^{+}\)=[M+H]⁺: 352.2060; found 352.2045.
10-Methyl-10-phenyl-5,10-dihydroindeno[1,2-b]indole (40p):

GP-1 was carried out with cinnamate 37g (95.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39p formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40p (93.0 mg, 63%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), \( R_f(37b)=0.51 \), \( R_f(40b)=0.36 \), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \( \nu_{\text{max}}=3412, 2925, 1599, 1495, 1441, 1315, 1247, 1018, 741 \) cm\(^{-1}\).

**\(^1\)H-NMR (CDCl\(_3\), 400 MHz)**: \( \delta=8.35 \) (br. s, 1H, NH), 7.44 (d, 1H, \( J=7.9 \) Hz, Ar-H), 7.43–7.36 (m, 5H, Ar-H), 7.27 (d, 1H, \( J=7.9 \) Hz, Ar-H), 7.25–7.13 (m, 5H, Ar-H), 7.07 (dd, 1H, \( J=7.5 \) and 7.4 Hz, Ar-H), 1.96 (s, 3H, Ar-C-CH\(_3\)) ppm.

**\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz)**: \( \delta=158.6 \) (s, Ar-C), 144.2 (s, Ar-C), 140.9 (s, Ar-C), 133.2 (s, Ar-C), 129.6 (s, Ar-C), 128.3 (d, 2C, Ar-CH), 126.8 (d, Ar-CH), 126.4 (d, Ar-CH), 125.8 (d, Ar-CH), 121.8 (s, Ar-C), 120.7 (s, Ar-C), 120.3 (d, Ar-CH), 118.8 (d, Ar-CH), 117.6 (d, Ar-CH), 115.3 (d, Ar-CH), 112.1 (d, Ar-CH), 50.6 (s, Ar-C-CH\(_3\)), 24.4 (q, Ar-C-CH\(_3\)) ppm.

**HR-MS (ESI\(^+\))**: \( m/z \) calculated for \([C_{22}H_{18}N]^+=[M+H]^+\): 296.1434; found 296.1422.
10-(4-Chlorophenyl)-10-methyl-5,10-dihydroindeno[1,2-b]indole (40q):

GP-1 was carried out with cinnamate 37h (112.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39q formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40q (103.9 mg, 63%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), \( R_f \) (37h)=0.52, \( R_f \) (40q)=0.36, UV detection].

\[
\begin{align*}
\text{IR (neat; MIR-ATR, 4000–600 cm}^{-1} &\text{): } \nu_{\text{max}}=3406, 2925, 1604, 1489, 1441, 1310, 1246, 1094, 1012, 819, 741 \text{ cm}^{-1}. \\
\text{\( ^1H-NMR \) (CDCl}_3, 400 MHz): } \delta=8.37 \text{ (br. s, 1H, NH), 7.45 (dd, 2H, } J=7.8 \text{ and 7.3 Hz, Ar-H), 7.35 \text{ (d, 1H, } J=7.8 \text{ Hz, Ar-H), 7.35–7.24 (m, 4H, Ar-H), 7.22–7.12 (m, 4H, Ar-H), 7.08 \text{ (dd, 1H, } J=7.8 \text{ and 7.3 Hz, Ar-H), 1.94 \text{ (s, 3H, Ar-C-CH}_3) ppm.} \\
\text{\( ^{13}C-NMR \) (CDCl}_3, 100 MHz): } \delta=158.2 \text{ (s, Ar-C), 142.8 \text{ (s, Ar-C), 141.0 \text{ (s, Ar-C), 140.8 \text{ (s, Ar-C), 133.1 \text{ (s, Ar-C), 132.1 \text{ (s, Ar-C), 130.9 \text{ (s, Ar-C), 128.4 \text{ (d, 2C, Ar-CH), 127.8 \text{ (d, 2C, Ar-CH), 127.0 \text{ (d, Ar-CH), 125.9 \text{ (d, Ar-CH), 123.9 \text{ (d, Ar-CH), 123.4 \text{ (s, Ar-C), 122.0 \text{ (d, Ar-CH), 120.4 \text{ (d, Ar-CH), 118.6 \text{ (d, Ar-CH), 117.8 \text{ (d, Ar-CH), 112.2 \text{ (d, Ar-CH), 50.1 \text{ (s, Ar-C-CH}_3), 24.2 \text{ (q, Ar-C-CH}_3) ppm.} \\
\text{HR-MS (APCI\textsuperscript{+}): } m/z \text{ calculated for } [C_{22}H_{17}ClN]^{+}[M+H]^+: 330.1044; \text{ found 330.1034.}
\end{align*}
\]
10-(4-Bromophenyl)-10-methyl-5,10-dihydroindeno[1,2-b]indole (40r):

GP-1 was carried out with cinnamate 37i (134.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39r formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40r (102.9 mg, 55%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), \( R_f(37i)=0.54, R_f(40r)=0.38 \), UV detection].

**IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\))**: \( \nu_{max}=3401, 2925, 1599, 1487, 1444, 1390, 1315, 1078, 1008, 745 \text{ cm}^{-1} \).

**\(^1H\)-NMR (CDCl\(_3\), 400 MHz)**: \( \delta=8.42 \text{ (br. s, 1H, NH)}, 7.45 \text{ (ddd, 2H, } J=7.8, 7.3 \text{ and } 1.0 \text{ Hz, Ar-H)}, 7.39–7.26 \text{ (m, 5H, Ar-H)}, 7.24–7.12 \text{ (m, 4H, Ar-H)}, 7.09 \text{ (ddd, 1H, } J=8.3, 7.8 \text{ and } 1.0 \text{ Hz, Ar-H}), 1.94 \text{ (s, 3H, Ar-C-CH}_3\text{)} \text{ ppm} \).

**\(^{13}C\)-NMR (CDCl\(_3\), 100 MHz)**: \( \delta=158.1 \text{ (s, Ar-C)}, 143.4 \text{ (s, Ar-C)}, 141.0 \text{ (s, Ar-C)}, 140.8 \text{ (s, Ar-C)}, 133.1 \text{ (s, Ar-C)}, 131.4 \text{ (d, 2C, Ar-CH)}, 130.8 \text{ (s, Ar-C)}, 129.6 \text{ (s, Ar-C)}, 128.2 \text{ (d, 2C, Ar-CH)}, 127.0 \text{ (d, Ar-CH)}, 125.9 \text{ (d, Ar-CH)}, 123.9 \text{ (d, Ar-CH)}, 122.0 \text{ (d, Ar-CH)}, 120.4 \text{ (d, Ar-CH)}, 118.6 \text{ (d, Ar-CH)}, 117.8 \text{ (d, Ar-CH)}, 115.3 \text{ (s, Ar-C)}, 112.2 \text{ (d, Ar-CH)}, 50.1 \text{ (s, Ar-C-CH}_3\text{)}, 24.2 \text{ (q, Ar-C-CH}_3\text{)} \text{ ppm} \).

**HR-MS (ESI\(^+\))**: m/z calculated for [C\(_{22}\)H\(_{16}\)BrN]\(^+\)=[M]\(^+\): 373.0466; found 373.0454.
10-(4-Chlorophenyl)-3,10-dimethyl-5,10-dihydroindeno[1,2-b]indole (40s):

GP-1 was carried out with cinnamate 37h (112.0 mg, 0.50 mmol), toluene (552.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39s formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40s (103.1 mg, 60%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), \( R_f \) (37h)=0.52, \( R_f \) (40s)=0.37, UV detection].

IR (neat; MIR-ATR, 4000–600 cm\(^{-1}\)): \( \nu_{\max } \)=3409, 2924, 1607, 1489, 1441, 1312, 1094, 1013, 744 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3, 400 \) MHz): \( \delta \)=8.35 (br. s, 1H, NH), 7.45 (d, 1H, \( J=8.3 \) Hz, Ar-H), 7.35 (d, 1H, \( J=7.8 \) Hz, Ar-H), 7.28–7.24 (m, 3H, Ar-H), 7.22–7.14 (m, 4H, Ar-H), 7.08 (ddd, 1H, \( J=7.8, 7.3 \) and 1.0 Hz, Ar-H), 6.99 (d, 1H, \( J=7.8 \) Hz, Ar-H), 2.40 (s, 3H, Ar-CH\(_3\)), 1.93 (s, 3H, Ar-C-CH\(_3\)) ppm.

\(^{13}\)C-NMR (CDCl\(_3, 100 \) MHz): \( \delta \)=155.4 (s, Ar-C), 143.1 (s, Ar-C), 140.9 (s, Ar-C), 140.8 (s, Ar-C), 136.8 (s, Ar-C), 133.2 (s, Ar-C), 132.0 (s, Ar-C), 131.2 (s, Ar-C), 128.4 (d, 2C, Ar-CH), 127.7 (d, 2C, Ar-CH), 126.6 (d, Ar-CH), 123.6 (d, Ar-CH), 123.4 (d, Ar-CH), 121.9 (d, Ar-CH), 120.4 (d, Ar-CH), 118.6 (d, Ar-CH), 118.5 (d, Ar-CH), 112.2 (d, Ar-CH), 49.8 (s, Ar-C-CH\(_3\)), 24.2 (q, Ar-C-CH\(_3\)), 24.2 (q, Ar-CH\(_3\)) ppm.

HR-MS (ESI\(^+\)): m/z calculated for [C\(_{23}\)H\(_{18}\)ClN\(^+\)]=[M\(^+\)]: 343.1128; found 343.1121.
10-(4-Bromo-2-methoxyphenyl)-10-methyl-5,10-dihydroindeno[1,2-b]indole (40t):

GP-1 was carried out with cinnamate 37g (95.0 mg, 0.50 mmol), 3-bromoanisole (139.4 mg, 0.75 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone 39t formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system 40t (110.0 mg, 59%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(37g)=0.65, R_f(40t)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–6000 cm⁻¹): \( \nu_{\text{max}} = 3410, 2964, 1602, 1485, 1458, 1441, 1390, 1242, 1023, 908, 866, 738 \text{ cm}^{-1} \).

\(^1H\)-NMR (CDCl₃, 400 MHz): \( \delta = 8.35 \text{ (br. s, 1H, NH)}, 7.46 \text{ (d, 1H, } J=7.3 \text{ Hz, Ar-H)}, 7.40 \text{ (d, 1H, } J=8.3 \text{ Hz, Ar-H)}, 7.39 \text{ (d, 1H, } J=7.3 \text{ Hz, Ar-H)}, 7.33–7.22 \text{ (m, 3H, Ar-H)}, 7.14 \text{ (d, 1H, } J=7.3 \text{ Hz, Ar-H)}, 7.12 \text{ (d, 1H, } J=7.3 \text{ Hz, Ar-H)}, 7.05 \text{ (dd, 1H, } J=7.8 \text{ and } 7.3 \text{ Hz, Ar-H)}, 6.97 \text{ (dd, 1H, } J=8.3 \text{ and } 2.0 \text{ Hz, Ar-H)}, 6.89 \text{ (d, 1H, } J=2.0 \text{ Hz, Ar-H)}, 3.45 \text{ (s, 3H, ArOCH₃)}, 1.93 \text{ (s, 3H, Ar-C-CH₃)} \text{ ppm.}

\(^{13}C\)-NMR (CDCl₃, 100 MHz): \( \delta = 159.2 \text{ (s, Ar-C)}, 158.4 \text{ (s, Ar-C)}, 140.9 \text{ (s, Ar-C)}, 140.6 \text{ (s, Ar-C)}, 133.3 \text{ (s, Ar-C)}, 131.7 \text{ (s, Ar-C)}, 130.4 \text{ (s, Ar-C)}, 129.7 \text{ (d, Ar-CH)}, 126.6 \text{ (d, Ar-CH)}, 125.5 \text{ (d, Ar-CH)}, 123.6 \text{ (s, Ar-C)}, 123.5 \text{ (d, Ar-CH)}, 123.4 \text{ (d, Ar-CH)}, 121.5 \text{ (d, Ar-CH)}, 121.0 \text{ (s, Ar-C)}, 120.1 \text{ (d, Ar-CH)}, 118.7 \text{ (d, Ar-CH)}, 117.4 \text{ (d, Ar-CH)}, 115.8 \text{ (d, Ar-CH)}, 112.1 \text{ (d, Ar-CH)}, 55.6 \text{ (q, Ar-OCH₃)}, 49.5 \text{ (s, Ar-C-CH₃)}, 24.7 \text{ (q, Ar-C-CH₃)} \text{ ppm.}
HR-MS (ESI⁺): m/z calculated for \([C_{23}H_{22}{^8}BrN_2O]^+=[M+NH_4]^+\): 423.0890; found 423.0912.

\(^1\)H-NMR (400 MHz) spectrum of 40b in CDCl₃

\(^{13}\)C-NMR (100 MHz) spectrum of 40b in CDCl₃
$^1$H-NMR (400 MHz) spectrum of 40m in CDCl$_3$
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LIST OF PUBLICATIONS


6. A facile, superacid promoted sequential domino one-pot dual C-C bond formation and fischer indole synthesis: Rapid access to 10-phenyl-5,10-dihydroindeno[1,2-b]-indoles, **A. G. K. Reddy** and G. Satyanarayana (manuscript submitted).


REFERENCES AND NOTES:


